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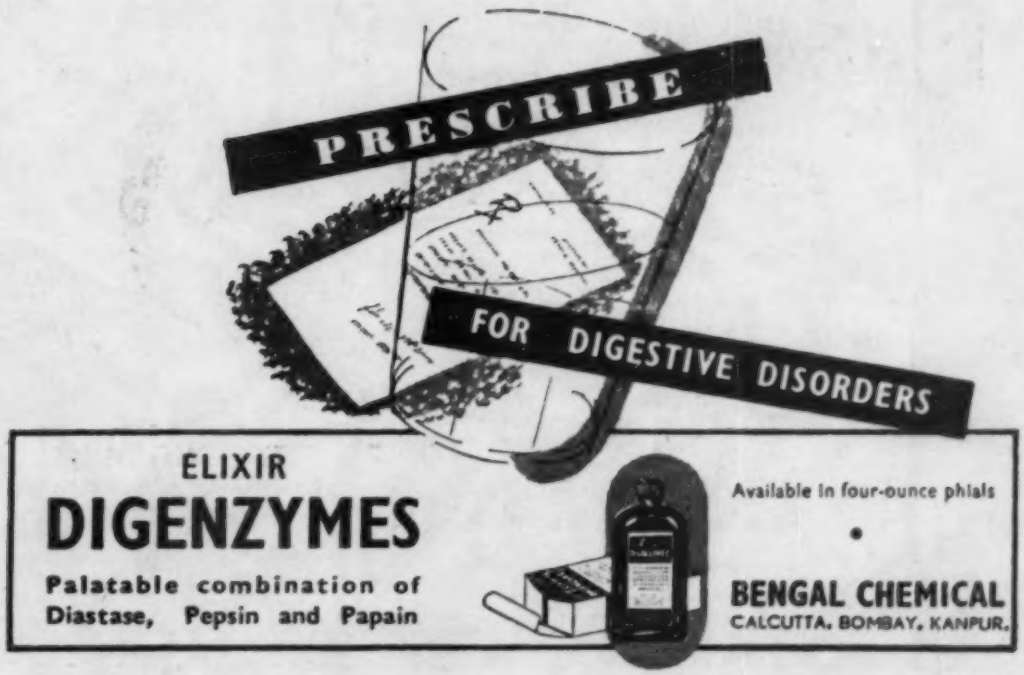

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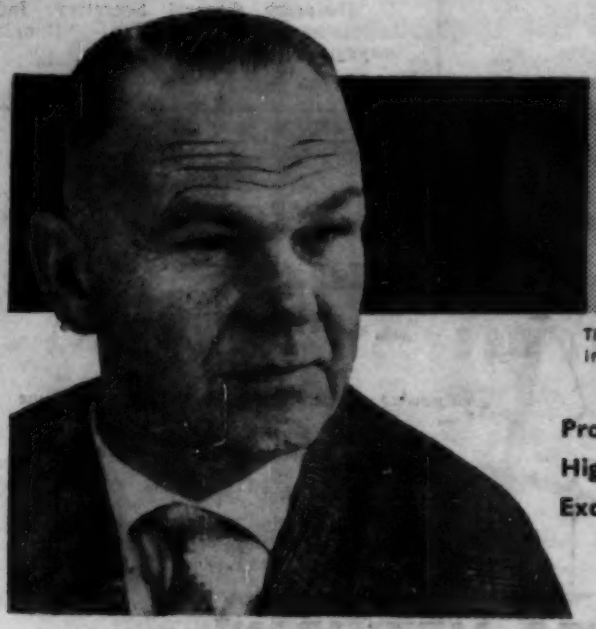

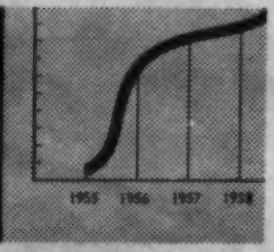

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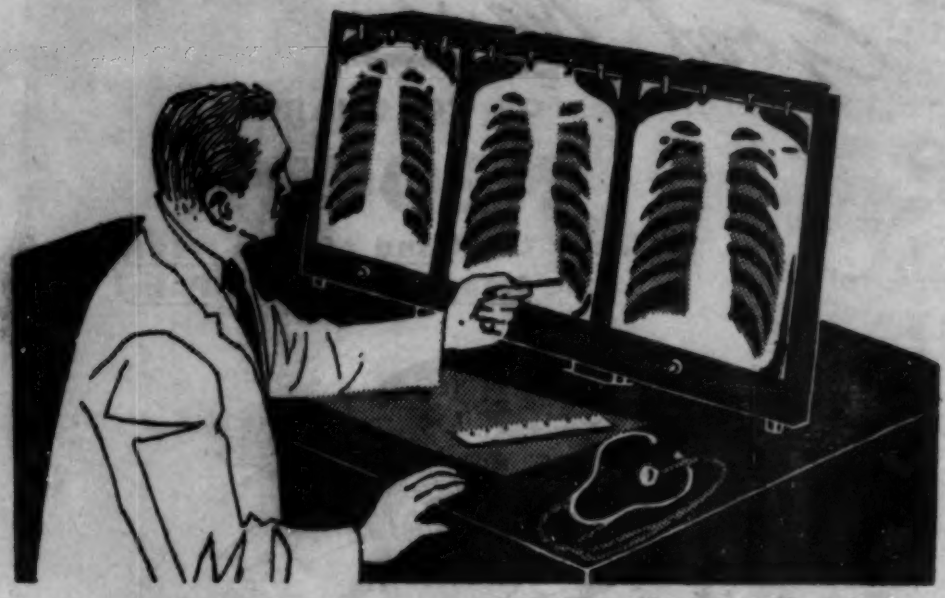

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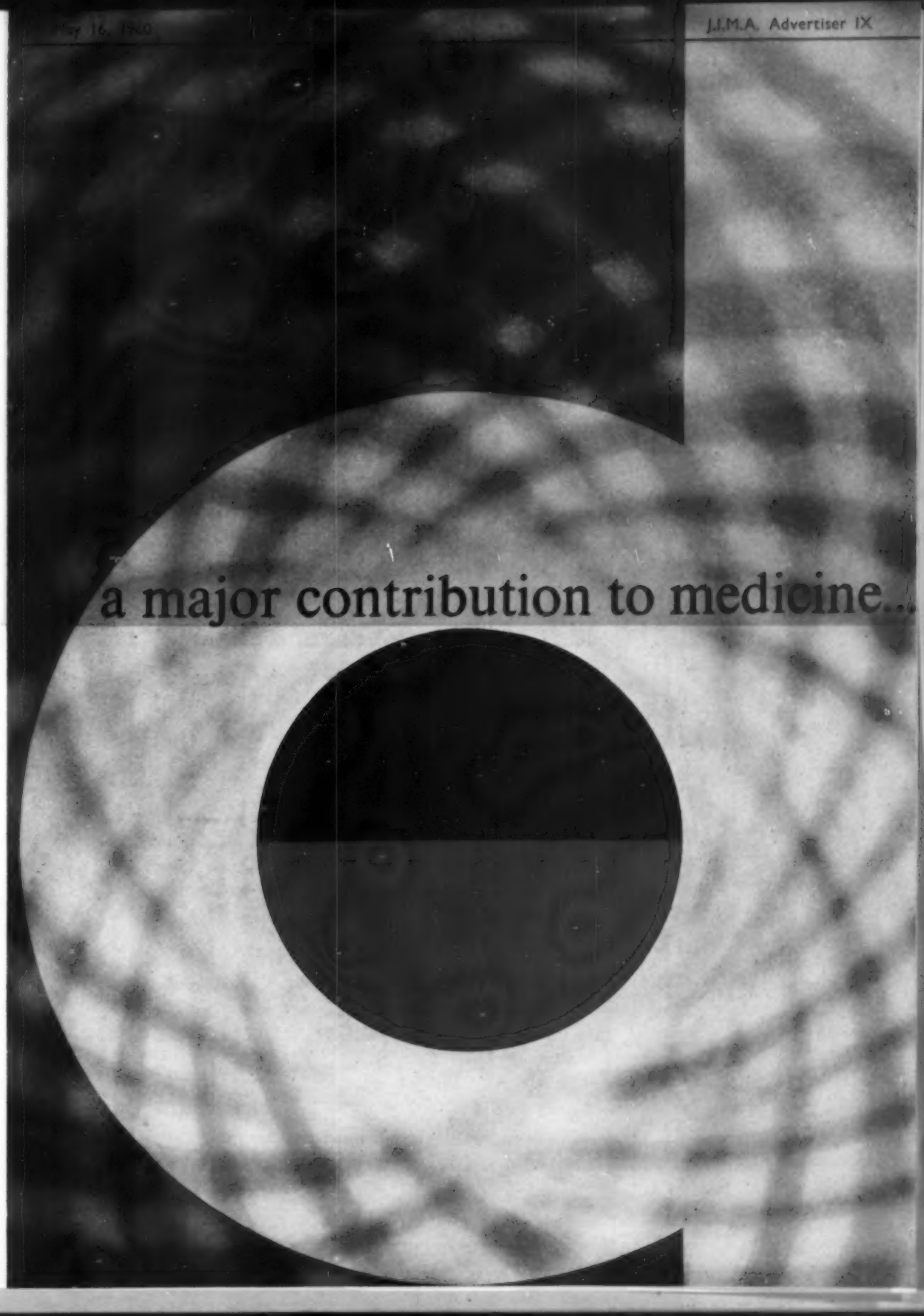
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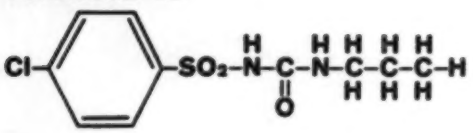

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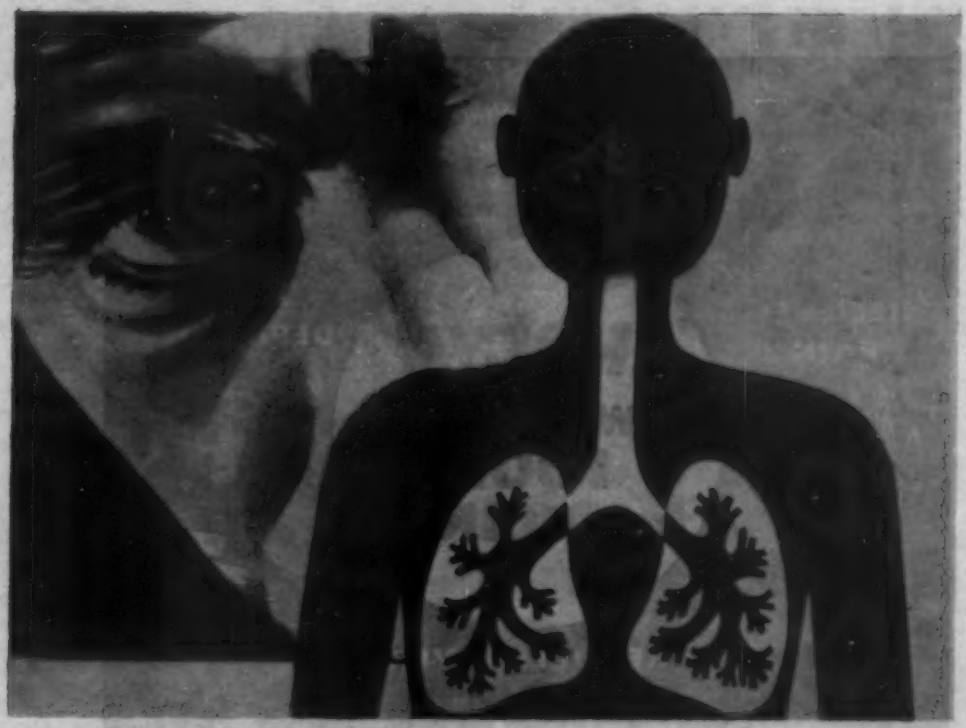

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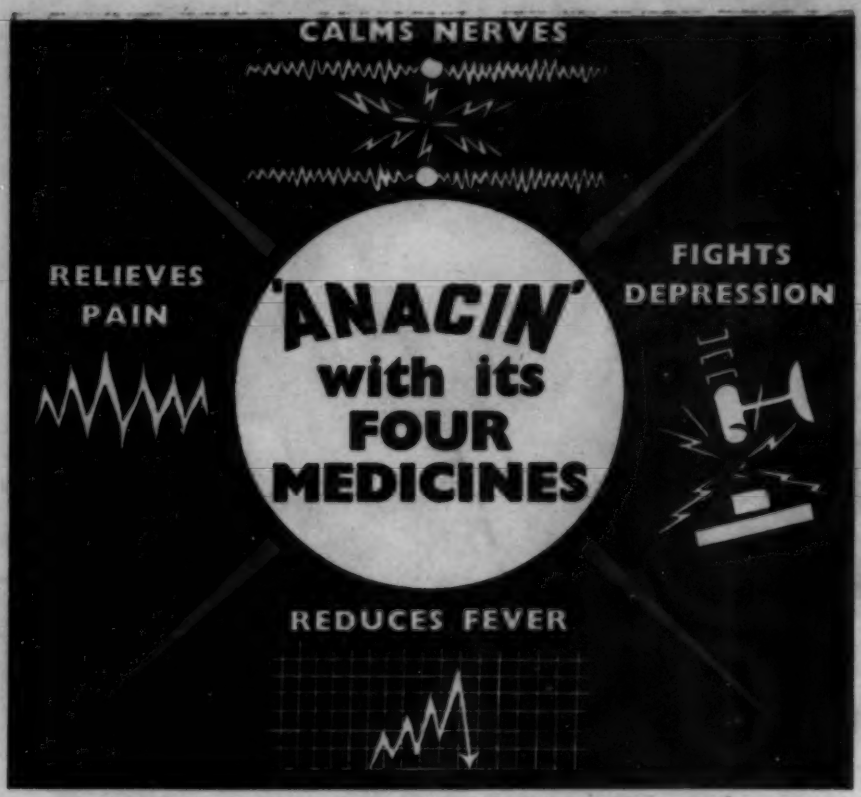

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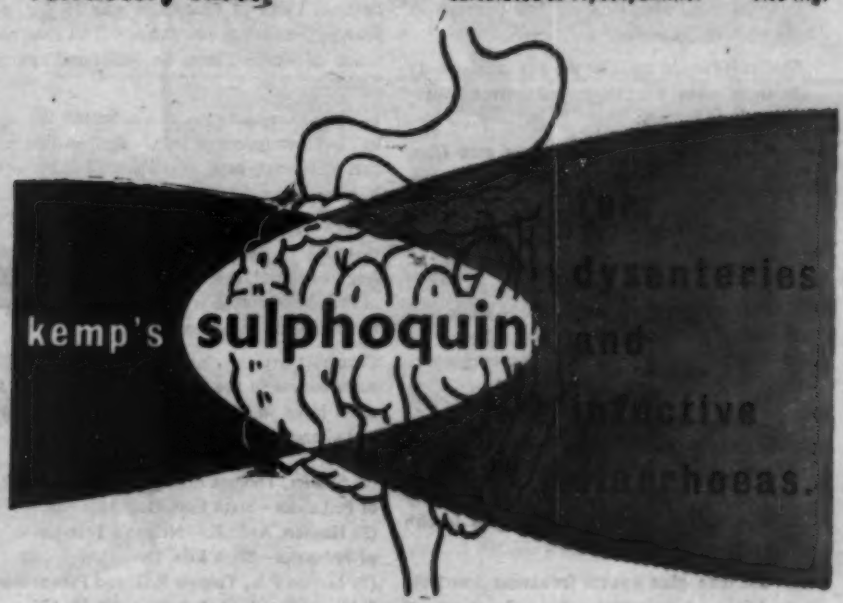

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Nutritional requirements of children

Children, like adults, require food for strength and for replacing lost energy. In childhood, there is an additional demand for food to support growth. According to Shaffer many children do not get the right kind of diet owing to parents' lack of knowledge, economic restrictions or traditional eating habits.

Serious illnesses can be prevented by making sure that children get sufficient calories and a balanced diet—which means, of course, protein, fats, carbohydrates, vitamins and minerals in the right proportions.

Shaffer (1) would consider the diet satisfactorily balanced when the calories are derived approximately as follows:

15 per cent from protein, 60 per cent from carbohydrates and 25 per cent from fat.

According to Hansen (2), fats are important as a concentrated energy reserve, physical protection for blood vessels, nerves and organs; as insulation against changes in temperature; as a vehicle for absorbing vitamins (A, D, E and K). Fats also stimulate appetite, aid satiety by delaying the emptying time of the stomach and spare protein.

Among poor class children, especially in South India, dry and rough skin is common. The condition is usually attributed to vitamin A deficiency; but the observations of Menon, Tulpule and Patwardhan (3) suggest that dietary deficiency of fat may have something to do with this abnormality.

At one time, ghee was the fat almost invariably used for cooking purposes. But today more and more people are cooking with oil, particularly with partially hydrogenated vegetable oils. Deuel (4) has shown that the hydrogenated oils used in margarine and vanaspati are as good as natural oils and butter fat in nutritive value and in aiding growth, fertility and lactation. Nhavi and Patwardhan (5) confirm this.

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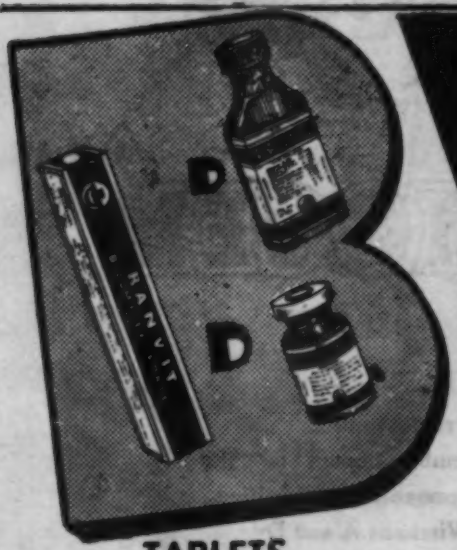

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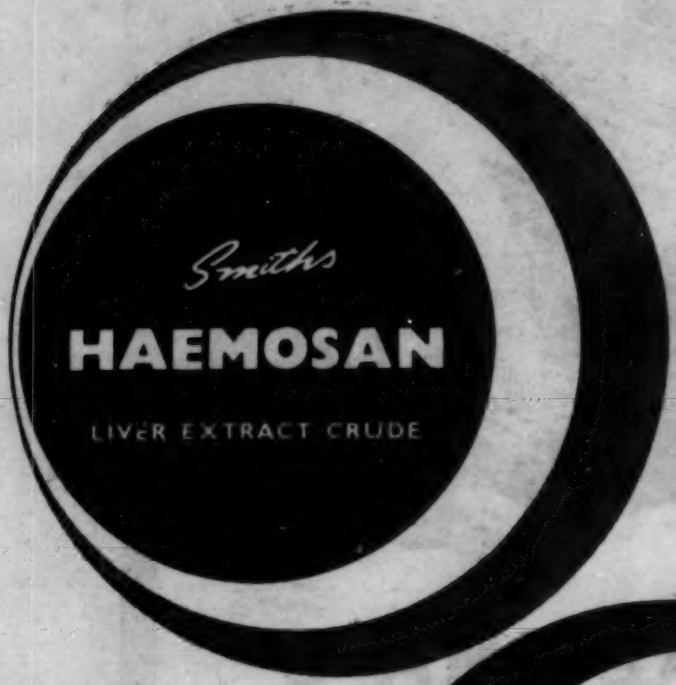

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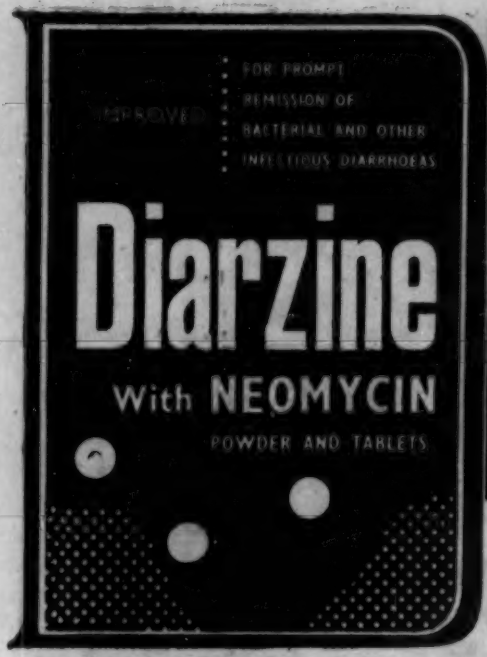

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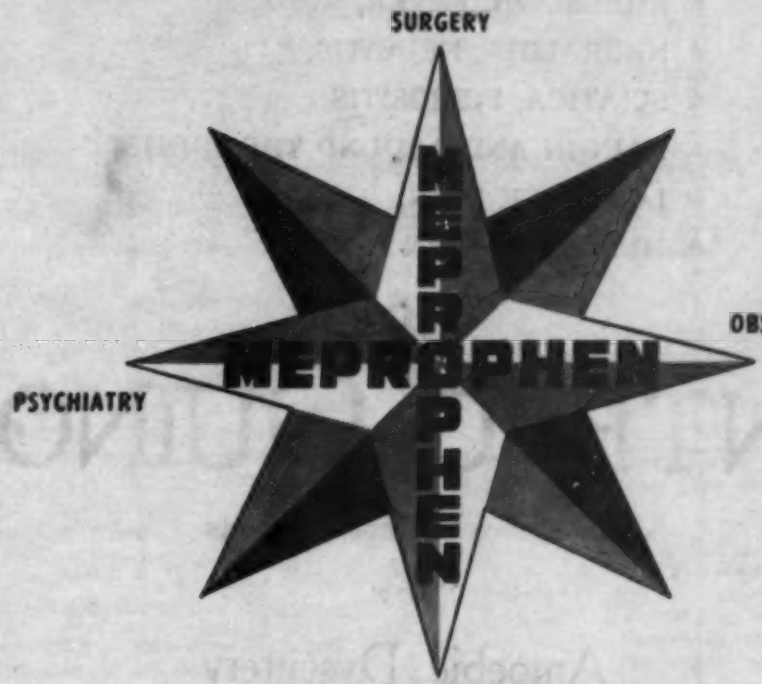

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ORIGINAL ARTICLES

CHRONIC MYELOID LEUKAEMIA: A STUDY OF 116 CASES

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Chronic myeloid leukaemia is the commonest type of leukaemia in Indians. In a series of 307 patients with leukaemia, chronic myeloid leukaemia accounted for 37·6 per cent of cases (Chatterjea, Ghose and Ray, 1959). During the last ten years, 116 cases of chronic myeloid leukaemia were investigated and treated in the haematology department of the School of Tropical Medicine, Calcutta. This communication presents our observations on the various aspects of these patients.

MATERIALS AND METHODS

Blood and bone marrow pictures were evaluated in the light of clinical data. Systematic clinical and relevant laboratory investigations were carried out to exclude the possibility of leukaemoid reaction. Final appraisal was made on follow-up study.

The following antileukaemic agents were employed for the control of the disease: (a) splenic irradiation; (b) busulphun (Myleran); (c) urethane, and (d) triethylene melamine (TEM). One agent was used at a time. A second agent was employed when there was evidence of resistance to the therapy first administered.

OBSERVATIONS

AETIOLOGY:

Age—The ages of the patients varied from 3 to 82 years with a mean age of 34·5 years. There were only three children below 12 years (aged 3, 5½ and 11 years). The maximum number of cases was in the age-group between 23 and 32 years.

Sex—Males were affected more frequently than females, the ratio of male: female being 1·6: 1.

Religion—There were 103 Hindus, 8 Mohammedans, 4 Christians and 1 Sikh.

Economic status—According to the per capita monthly income, the cases were divided into four groups as follows:

Groups			Per capita monthly income
A	...	...	Rs. 100/- or more
B	...	...	between Rs. 50/- and Rs. 99/-
C	...	...	between Rs. 20/- and Rs. 49/-
D	...	...	less than Rs. 20/-

Out of a total of 73 cases in which dependable data were available, cases in different groups, viz., A, B, C and D, were 7, 4, 20 and 42 respectively.

Residence—Reliable data were available in 90 cases of whom 44 were residents in urban and 46 in rural areaes.

Diet—Out of a total of 98 cases in which reliable data were available, only 11 were vegetarians, the rest had been taking a mixed diet.

Occupation—Out of a total of 50 male patients from whom reliable data were obtained, 17 were petty businessmen, 7 belonged to the engineering and allied trade or profession, 7 held clerical jobs, 7 were domestic servants or office boys, 6 cultivators, 2 physicians, 2 teachers and 2 students. All the female patients were housewives except 4.

Two of these female patients were school teachers; one was a student and the other a stenographer.

MODE OF ONSET AND MAIN SYMPTOM AT ONSET:

The onset was insidious in all the cases except in one child aged 3 years.

The main symptom at onset could be ascertained in 104 cases, each patient being grouped under one symptom only. The commonest mode of onset was with splenomegaly and in 35 patients this was the main symptom at onset. In 33 patients, asthenia was the chief symptom and in 26 fever was the initial symptom. Two patients complained of pain in the bones, 2 of pain in the abdomen, 2 of anorexia and one each of loss of weight, headache, lymphadenopathy and palpitation on exertion as the chief symptom at onset.

The chief complaints with which the patients presented themselves at the time of first attendance were also recorded and the total number of patients under each of the symptoms was as follows:

Asthenia 66, splenomegaly 64, fever 57, pain in abdomen 26, dyspepsia 17, loss of weight 10, cough 8, dysentery 7, headache 6, pain in the bone 6, palpitation on exertion 6, haemorrhages 5, dyspnoea 4, lymphadenopathy 4, pallor 3, amenorrhoea 2, tingling sensation over different parts of the body 2, swelling of legs and feet 1, polyuria 1 and glossitis 1.

DURATION OF SYMPTOMS PRIOR TO DIAGNOSIS:

Analysis of data pertaining to the probable duration of the disease (prior to diagnosis as judged from symptoms) and the period of survival indicate that early diagnosis, even when followed by timely therapy, did not necessarily ensure prolongation of life span. Thus a patient with 1·5 months' duration of symptoms due to leukaemia had a period of survival of only 26·5 months; while another patient suffering for 36 months, prior to diagnosis of leukaemia, had a total period of survival of 96 months. This finding is in agreement with the views of Hambly and Robertson (1959).

CARDINAL CLINICAL FEATURES:

The cardinal clinical features detected at the *time of first attendance* were splenomegaly, hepatomegaly, lymphadenopathy and haemorrhages. The incidence of these features was as follows:

Splenomegaly—The spleen was enlarged and palpable in all the cases, excepting one. The patient without any palpable splenic enlargement was a 36-year old female with a total W.B.C. count of 57,500/c.mm. The degree of enlargement was as follows: 'just palpable' to 5 cm. below the costal margin 13, 5·1 to 10 cm. 32, 10·1 to 15 cm. 25, 15·1 to 20 cm. 19, 20·1 to 25 cm. 18, 25·1 to 30 cm. 7 and greater than 30 cm. 1 case.

Hepatomegaly—The liver was enlarged in 108 patients and the degree of enlargement was as follows: 'just palpable' to 5 cm. below the costal margin 84, 5·1 to 10 cm. 23, 10·1 to 15 cm. 1 case.

Lymphadenopathy—Enlargement of the superficial group of lymph nodes was present in 12 per cent of cases. The enlargement was usually regional, being generalised in only three cases. The degree of enlargement was significant in 5 per cent of cases, the maximum size of the lymph nodes being 2·5 cm. × 2·5 cm. In the remaining 7 per cent of cases the size of the lymph nodes varied from 0·6 cm. × 0·6 cm. to 0·8 cm. × 0·8 cm.

Haemorrhages—Bleeding manifestations were present in 8 per cent of the cases at the time of first attendance.

SALIENT HAEMATOLOGICAL FINDINGS AT THE FIRST ATTENDANCE:

Haemoglobin varied from 2·9 to 16·5 g. per cent.

Total W.B.C. varied from 25,200 to 460,000 per c.mm., myeloblasts varied from 1 to 9 per cent, myelocytes varied from 1 to 49·4 per cent, metamyelocytes varied from 0 to 31 per cent, eosinophils varied from 0 to 10 per cent and basophils varied from 0 to 18 per cent.

Thrombocytes varied from 15,600 to 1,752,000 per c.mm. Significant thrombocytopenia (platelet count below 100,000 per c.mm.) was observed in only 3 patients.

OTHER CONDITIONS ASSOCIATED WITH LEUKAEMIA:

In this series, 3 patients had diabetes mellitus associated with leukaemia. The onset of diabetes preceded that of leukaemia by 4 and 12 months in 2 patients. In the third patient, both the conditions were diagnosed simultaneously.

There was a history of antecedent or coincident tuberculosis in 4 patients. In one case, a girl aged 11 years, leukaemia was complicated with tuberculous lymphadenitis. In the remaining 3 (all males) aged 40, 45 and 50 years, pulmonary tuberculosis preceded the onset of leukaemia by 14, 23 and 29 months respectively.

Out of a total of 43 female patients of childbearing age, only three conceived during the period of observation. Two of the latter were in states of remission during the periods of gestation. All of them had normal deliveries and the children were normal.

MODES OF TERMINATION :

The causes of death, as obtained from a final follow-up of 32 patiets, were as follows :

'Blast' crisis (20), progressive anaemia (3), myocardial infarction (2), bone marrow failure (2), hypoproteinaemia with ascites (1). Four patients died of unrelated or unexplained causes.

VITAMIN B_{12} LEVEL IN SERUM :

Both free and total serum vitamin B_{12} levels were assayed by the microbiological method using *Euglena gracilis* var *bacillaris* as the test organism (Ross, 1952). The initial free serum B_{12} level, as estimated in 48 patients, varied from <20 to 1,640 $\mu\mu$g/ml. with a mean of 415·8 $\mu\mu$g/ml. and the initial total serum B_{12} level as estimated in 48 patients, varied from 480 to 9,400 $\mu\mu$g/ml. with a mean of 3,084·9 $\mu\mu$g/ml. With this method in normal Indian subjects, the free serum vitamin B_{12} varies from 0 to 157 $\mu\mu$g/ml. with a mean of 33$\mu\mu$g/ml. and the total serum B_{12} varies from 98 to 940 $\mu\mu$g/ml. with a mean of 281·9 $\mu\mu$g/ml. (Chatterjea, Banerjee, Ghose and Chaudhuri, 1959).

RESPONSE TO THERAPY :

Myleran—A total of 46 patients in 2 broad groups were treated with myleran. Group A : In 23 patients this was the only therapy ever used. Group B : In 23 patients myleran therapy was either preceded or followed by other forms of therapy, viz., deep x-ray, urethane or TEM.

During the earlier part of the study, therapy was started with a daily dosage of 4 mg. given orally in 2 divided doses. The response obtained with this dosage was found to be rather slow. In most of the cases, depending on the initial white cell count, treatment was started with a dosage of 8 to 12 mg. daily. This was reduced to 2 to 4 mg. when the white cell count had fallen to a level between 40,000 and 60,000 per c.mm. The therapy was continued till the white cell count had fallen to 10,000 per c.mm. or thereabout. No further treatment by way of maintenance was usually given as long as the patient was symptom-free and the total white cell count was within 50,000 per c.mm. Treatment with a dosage of 2 to 4 mg. daily was usually re-instituted when a rising white cell count was associated with fever, weakness, enlargement of the spleen and other symptoms.

In the above series of 46 patients, remission was obtained in 38. The period of remission varied from 0·3 to 29 months, with a mean of 6·5 months.

Of the 8 patients not responding to myleran therapy, 2 received myleran for the first time (primary resistance) the remaining 6 being treated previously with deep x-ray, urethane or TEM. One of the two patients showing primary resistance to myleran ultimately developed 'blast crisis' within 3½ months of first attendance. He complained of nausea, vomiting and arthralgia which continued unabated throughout the course of his illness. The second patient, however, showed a temporary response to a subsequent course of deep x-ray. Both of these patients were aged 32 years ; the duration of illness prior to therapy was 10 months and 2 years respectively. The details of 6 patients who had been treated previously with other forms of therapy were as follows : 3 had only deep x-ray, 2 had deep x-ray in combination with urethane and TEM and one received TEM and urethane prior to myleran therapy. The ages of these patients varied from 25 to 39 years. The duration of illness prior to therapy varied from 3 months to 3 years. Lymph nodes were enlarged in 3 cases, enlargement being significant in 2 cases. Only one patient showed haemorrhagic manifestations. One patient, aged 26 years, developed pleurisy during the course of the illness (after the initiation of therapy).

Deep x-ray—A total of 40 patients in 2 groups were treated with splenic irradiation. Group A : In 12 patients this was the only form of therapy ever used. Group B : In 28 patients, deep x-ray therapy was either preceded or followed by other forms of therapy, viz., myleran, urethane or TEM.

Deep x-ray therapy was given usually in the dose of 96γ daily for 3 consecutive days in one week. Depending on the initial clinical and haematological status as also the response to therapy, 6 to 18 exposures were usually given in one course. Therapy was continued till the total W.B.C. count had dropped to a level ranging from 15,000 to 30,000 per c.mm. In the above series of 40 patients, remission was obtained in 37 patients. The period of remission varied from 1 to 34 months with a mean of 9·7 months.

The details of 3 patients not responding to deep x-ray therapy were as follows : the ages of these patients varied from 30 to 45 years. The duration of illness prior to therapy varied from 4 to 7 months. One of these patients had asthma associated with leukaemia. One patient received deep x-ray for the first time, one received urethane only for 4 days prior to deep x-ray and the third patient had TEM and urethane prior to deep x-ray.

Urethane—A total of 23 patients in two groups were treated. Group A : In 6 patients, this was the only form of therapy ever used. Group B : In

17 patients, urethane therapy was preceded or followed by other forms of therapy, viz., deep x-ray, myleran or TEM.

Urethane was administered in gelatin capsule, usually in the dosage of 1 to 2 g. daily. Higher dosages were not tolerated. Depending on the clinical and haematological response, the treatment was continued with dosages adjusted as necessary till a remission was obtained. Thereafter small maintenance dose was prescribed to fortify the remission.

In the above series of 23 patients, satisfactory remission could be induced and maintained in only 9 patients. The period of remission varied from 0·5 to 42·5 months with a mean of 12 months.

The details of the 14 patients not showing any remission were as follows: the ages of these patients varied from 24 to 82 years. The duration of illness prior to therapy varied from 2 months to 4 years. Five patients showed haemorrhagic manifestations, one having leukaemia associated with diabetes mellitus. One patient had enlarged inguinal lymph nodes and one showed thrombocytopenia. In 4 patients urethane was the first agent employed; two of these later responded to deep x-ray and myleran. The remaining 10 patients had previously shown one or two remissions with deep x-ray or TEM.

TEM—Seven cases were treated with TEM. Four patients received the therapy for the first time. Two patients had urethane and one had myleran and deep x-ray in the past. TEM was given in a dosage of 5 mg. daily for 3 to 15 days. One patient had 3 courses of TEM therapy. Slight nausea and vomiting were observed in a few cases but this did not interfere with the continuation of TEM therapy. The response to TEM was favourable in 4, slight in one and inconclusive in 2 cases.

SIDE EFFECTS OF THE DRUGS USED:

Myleran—Myleran was usually tolerated fairly well by these patients. Six patients complained of slight gastrointestinal intolerance manifested by one or two of the following symptoms: anorexia, nausea, vomiting, diarrhoea or pain in the abdomen. Gastrointestinal symptoms were never severe enough to warrant withdrawal of myleran therapy. Increased pigmentation of the skin occurred in as many as 8 patients. Amenorrhoea developed in 6 out of 13 women treated with myleran. Other side-effects included pruritus (2), alopecia (1) and paraesthesia (1). Thrombocytopenia was observed in only one patient.

'Blast crisis' developed in as many as 15 patients. In 5 of them, myleran was the only form of therapy ever used; others received deep x-ray, urethane or TEM in the past. The interval between the initiation of myleran therapy and the onset of 'blast crisis' varied from 1 to 48 months.

Deep x-ray—In the dosage schedule employed, deep x-ray appeared to be well tolerated. Ten out of 40 patients, however, complained of some sort of untoward symptoms. Side effects included anorexia, nausea and vomiting (2), diarrhoea (2), herpes zoster (1), pain over spleen (1), thrombocytopenia with ecchymoses (1), menorrhagia (1), melaena (1), weakness and giddiness (1) and allergic dermatitis (1). One of the patients developed 'blast crisis' during the period of therapy with deep x-ray.

Urethane—Nine out of 23 patients manifested symptoms and signs of intolerance. Intolerance was usually so marked as to necessitate discontinuation or reduction in the dosage of the drug. In as many as 7 patients, anorexia, nausea, and vomiting were the chief symptoms. Other side effects included dysentery (1), drowsiness (1), burning sensation (1). One patient developed infective hepatitis 14·5 months after the initiation of urethane therapy. 'Blast crisis' developed in 4 patients, three of whom were treated only with urethane.

'Blast crisis'—The term 'blast crisis' has been used to denote progressive increase of myeloblasts in blood and bone marrow, terminating in a picture more or less similar to that seen in acute leukaemia.

Thirty-two patients could be followed up till the termination; 20 in this group had developed 'blast crisis'. In 3 out of 20 patients, urethane was the only form of therapy used, while another patient received a course of deep x-ray prior to urethane therapy. The intervals between the initiation of urethane therapy and onset of 'blast crisis' were 11·5, 28 and 39 months in the patients receiving only urethane and 7·5 months in the patient treated with a course of deep x-ray previous to urethane therapy. One other patient, however, developed 'blast crisis' during deep x-ray therapy; he had been treated previously with one course each of deep x-ray and urethane; 'blast crisis' developed 13 days from the initiation of a second course of deep x-ray therapy. The remaining 15 patients had received myleran during some phase of the illness. Five of these 15 patients patients were treated only with myleran and the interval between the onset of 'blast crisis' and the initiation of myleran therapy varied from 1 to 23 months. Ten patients were treated previously with urethane, deep x-ray or TEM; the

TABLE 1—SHOWING COMPARATIVE RESPONSE TO URETHANE, DEEP X-RAY AND MYLERAN THERAPY

Therapy	Total duration of disease	No. in group	Duration prior to therapy in months			No. in whom remission obtained	Duration of remission in months			No. dead
			Minimum	Average	Maximum		Minimum	Average	Maximum	
Urethane	<1 year	0	—	—	—	—	—	—	—	—
	1—2 years	0	—	—	—	—	—	—	—	—
	2—3 ,,	1	—	12	—	1	—	8·5	—	1
	3—4 ,,	4	12	27	36	1	—	0·5	—	2
	4—5 ,,	1	—	54	—	1	—	5·0	—	—
	Total :	6		31		3		4·5		3
Deep x-ray	<1 year	2	1	3·5	6	2	1	3	5	—
	1—2 years	5	6	9·5	12	4	1	4	8	—
	2—3 ,,	2	18	19·5	24	2	2	3	4	1
	3—4 ,,	3	6	14	24	3	8	15·3	24	3
	Total :	12		11·6		11		6·3		4
Myleran	<1 year	4	1·5	3·4	4	4	0·3	1	2	1
	1—2 years	8	1	6·9	12	8	0·5	5·4	9·5	3
	2—3 ,,	7	1·5	16·5	24	6	1·5	6·4	13·5	2
	3—4 ,,	4	6	24	36	4	4·5	8·3	16	1
	Total :	23		12·7		22		5·3		7

interval between the onset of 'blast crisis' and initiation of myleran therapy varying from 1 to 48 months.

COMPARATIVE STUDY OF RESPONSE TO URETHANE, DEEP X-RAY AND MYLERAN THERAPY :

In the present series, a total of 109 patients were treated with urethane, deep x-ray or myleran singly or in combination. Comparative study on the relative merits of the three agents was made from an analysis of only those patients who had received one form of therapy. In this selected group there were 6 patients receiving urethane, 12 receiving deep x-ray and 23 receiving myleran therapy. The details of response to therapy in these 41 patients are shown in Table 1. From the point of view of tolerance and response to therapy, it appears that urethane was definitely inferior to both myleran and deep x-ray. Response to deep x-ray and myleran therapy appeared to be more or less similar.

DISCUSSION

Incidence of different types—The relative preponderance of the chronic myeloid type in our series (37·6 per cent) is in agreement with the findings of earlier workers of western countries (Panton and Valentine, 1929 ; Rosenthal and Harris, 1935 ; Leavell, 1938 ; Wintrobe 1942). According to many recent workers, chronic lymphocytic leukaemia in western countries is commoner than any other type (Best and Limarzi, 1952 ; Gauld *et al*, 1953). In MacMahon's series (1956), acute myeloid leukaemia was, however, the commonest type. In Gardikas, Leonard and Wilkinson's series (1955), chronic myeloid and chronic lymphocytic types showed more or less similar incidence.

Age—Chronic myeloid leukaemia was by far commoner in the adult (97·4 per cent). This findings is in agreement with observations of other workers (Ward, 1917 ; Wintrobe, 1942). The peak incidence in this series was in the age-group 23 to 32 years. Other workers had recorded peak incidence in later age groups, e.g., 30 to 35 years (Ward, 1917), 35 to 45 years (Minot *et al*, 1924 ; Hoffman and Craver, 1931 ; Leavell, 1938) and 45 to 50 years (Gauld *et al*, 1953).

Sex—The preponderance of males (1·6 : 1) in the present series is in agreement with the findings of Minot *et al* (1924) ; Hoffman and Craver (1931) and Leavell (1938). In the series of Best and Limarzi (1952), Gauld *et al* (1953) and Gardikas *et al* (1955), made preponderance was insignificant. In the present series, the predominance of males may, however, be more apparent than real. On the basis of the larger number of male patients attending the outpatients' department as also the greater number of indoor beds in the hospital for male patients, the incidence in favour of males might have been unduly weighed.

Environmental factors—The incidence of leukaemia has been claimed to be influenced by environmental conditions. Leukaemia has been reported to be more frequent in the rich than in the poor (Sacks and Seeman, 1947). Urbanisation has been claimed to be associated with the increasing incidence of leukaemia (Meadors, 1956). But in the present series neither the socio-economic status nor the place of residence, dietary habits, occupation, infection, exposure to myelotoxic agents appeared to have any aetiologic significance.

Radiation—Irradiation has been incriminated as a leukaemogenic agent (Kaplan, 1954). Leukaemia has been described in persons exposed to x-ray for variable lengths of time (Dunlap, 1942 ; Ulrich, 1946 ; March, 1950 ; Peller and Pick, 1952 ; van Swaay, 1955 ; Court-Brown and Abbat, 1955 ; Moloney, 1955 ; Simpson *et al*, 1955 ; Court-Brown and Doll, 1957). In the present series, radiation was unlikely to have played any causal role (Chatterjea, 1959).

Serum vitamin B_{12}—Abnormally high levels of total serum vitamin B_{12} corroborate the findings of previous workers (Beard *et al*, 1954 ; Mollin and Ross, 1955 ; Das Gupta *et al*, 1956 ; Rachmilewitz *et al*, 1957). Consistent with the views of these workers, with clinical and haematological improvement, the total serum vitamin B_{12} level tended to decline. Studies on the vitamin B_{12} content of leucocytes and liver tissue, however, indicate that neither the leucocytes nor the liver tissue was the source of the elevated serum vitamin B_{12} concentration in chronic myeloid leukaemia (Banerjee, Ghose and Chatterjea, in the press). This instance of hypervitaminosis without alimentation has not been reported with reference to any other vitamin and is in a sense unique.

Pregnancy—The occurrence of normal pregnancies terminating in normal full-term deliveries in all the three instances of pregnancy associated with leukaemia, suggests that probably pregnancy has no significantly adverese effect on this type of leukaemia. This observation is in accord with that of Forkner (1938), Moloney *et al* (1939), Kerr *et al* (1954), Harris (1953) and Wintrobe (1956).

Treatment—Chronic myeloid leukaemia, like all other types of leukaemia, is still incurable. With judicious application of radiotherapy and/or myleran, worthwhile remissions are obtainable in the vast majority of cases. That patients under controlled therapy can now lead useful lives has been amply proved. It is, however, very doubtful whether absolute life-span has been increased. Myleran remains the best chemotherapeutic drug so far available. It continues to be a close rival of deep x-ray therapy but is not likely to replace it. Until a better drug is available, the specific treatment would be splenic irradiation and/or myleran, employed one after the other as necessary. Regarding the first therapy of choice there is really no agreed opinion. One school would prefer x-ray, initially, keeping myleran in reserve for use when radio-resistance has developed. The other school would start with myleran and stick to it as long as it is effective. Presently available data do not permit any definite conclusion being drawn in favour of either method of management.

Summary

Chronic myeloid leukaemia is the commonest type of leukaemia in Indians. Observations on a series of 116 patients investigated during the last ten years are recorded. The series included 3 children below 12 years of age. Maximum number of cases was seen between 23 and 32 years. Classified according to the monthly per capita income, a significantly large number of patients was seen in the poorer groups.

In the peripheral blood, myeloblasts varied from 1 to 9 per cent. Serum vitamin B_{12} level was elevated, mean values for free and total fractions being 415·8 (range <20 - 1,640) and 3,084·9 $\mu\mu$g./ml. (range 480 - 9,400) respectively.

Review of associated conditions revealed the presence of diabetes mellitus in 3, pulmonary tuberculosis in an equal number of cases and tuberculous lymphadenitis in one. Three female patients conceived during the period of observation.

Relative merits of therapy with splenic irradiation and myleran are discussed.

Acknowledgment

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CHLORAMPHENICOL WITH HYDROCORTISONE AS AN ADJUVANT IN THE TREATMENT OF ENTERIC FEVER

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Until 1948 there was no specific cure for enteric fever. Treatment with chloramphenicol is a specific form of therapy. The addition of hydrocortisone to chloramphenicol therapy of typhoid fever is a further advancement in cutting short the febrile period as well as the convalescence.

MATERIALS AND METHODS

Eighty-one cases of enteric fever were treated with chloramphenicol in a medical unit of Patna Medical College Hospital during the year 1958-59.

The patients complaining of high fever, headache, and bodyache, with flushed face, congested eyes, coated tongue with red margins were admitted into the hospital. A careful history of the present illness and a thorough clinical examination was done. The laboratory investigations included the total and differential white cell count soon after the admission. Blood culture was set up in patients who were admitted during the first week of the illness. In those who came in the second week and later, agglutination test was performed. The routine examination of urine was done in all cases. Intermittent rise of temperature in patients in the third or fourth week of their illness was indication for urine culture.

The patients were divided into five groups:

Group I consisted of 13 cases of enteric fever who were very toxic, had hyperpyrexia and several complications. They were treated with chloramphenicol V.F. and an adjuvant corticoid, hydrocortisone (cases of marked severity).

Group II consisted of 25 cases of enteric fever who were toxic, had hyperpyrexia, but had few or no complications. They were treated with chloramphenicol V.F. and hydrocortisone (cases of moderate severity).

Group III consisted of 18 cases similar to those of group II but treated with chloramphenicol V.F. only (cases of moderate severity).

Group IV consisted of 11 cases of enteric fever similar to those of group II and treated with chloramphenicol only.

Group V consisted of 14 cases of enteric fever which presented very few toxic features, and were

mild in nature. They were treated with chloramphenicol V.F. only.

Absolute rest in bed was enforced till convalescence was established. Due to anorexia, toxaemia, mental apathy and abdominal discomfort, in many cases, the ideal requirement of calories for typhoid fever, could not be given. However, every effort was made to achieve 1,500 calories of diet in the active stage of disease instead of 2,500 calories, i.e., 20 calories per pound body weight. This consisted mainly of milk, fruit juice, whey, glucose and vitamins. The feeds were given in smaller quantities every 3 hours.

Chloramphenicol was given as 250 mg. capsules—2 capsules to start with, followed by one capsule every four hours till the temperature remained normal for two to three days. Thereafter, chloramphenicol was given in the reduced dosage for a further period of five to six days. Hydrocortisone 25 mg. tablet was given, twice a day during the febrile period as an adjuvant. The patients in group I received a total of 500 mg. of hydrocortisone, of which 250 mg. was given during the average 4·8 days of febrile period, and the rest continued for the 5 days of afebrile period. In group II, a total of 400 mg. of hydrocortisone was given as an adjuvant therapy. Of this 200 mg. was given during the average 3·5 days of febrile period and the rest in the next 4 days of afebrile period. Side reactions like gastro- intestinal disturbances, skin rashes, glossitis, depression of bone marrow and peripheral circulatory failure were looked for during chloramphenicol therapy.

Observations

INCIDENCE :

The number of cases in the different age groups was as follows :

Age groups (in years)	Number of cases
14—20	42
21—30	25
31—40	7
41—50	3
51—60	4

CLINICAL FEATURES :

Group I—A clinical trial in 13 severe cases of enteric fever was done with chloramphenicol V.F. and hydrocortisone. Two cases had relapse and returned back for treatment. Lassitude (100 per cent), frontal headache (61·5 per cent), bodyache (30·8 per cent), anorexia (100 per cent), abdominal discomfort and gurgling (76·9 per cent), constipation (53·8 per cent), diarrhoea (30·7 per cent, cough (46·1 per cent), hiccough (7·6 per cent), semi-consciousness (46·1 per cent) disappeared during the course of therapy on the 7th, 5th, 4th, 6th, 6·5th, 6th, 5·5th, 13th, 4th, 4·5th day respectively.

Effect of this regime of therapy on the progress of physical findings was marked. Flushed face (92·3 per cent), coated tongue with red margins (100 per cent), congested eyes (46·1 per cent), slow pulse (84·6 per cent), rapid pulse (15·4 per cent), tumid and tender abdomen (69·2 per cent), tympanitis (23·0 per cent) and high temperature (100 per cent) disappeared on the 5th, 5th, 4th, 6·5th, 7·5th, 6th, 7·5th, 10th, 6th and 4·8th day of treatment respectively.

One patient came under treatment on the 6th day of his illness when blood culture for *Bacillus typhosus* was negative. The rest came during the 2nd and 3rd weeks of their illness. The agglutination test was positive in 9 (69·2 per cent) and negative in 4 (30·8 per cent) cases. During the course of chloramphenicol therapy the usual rising titre was not seen.

Group II—A clinical trial in 25 moderate cases of enteric fever treated with chloramphenicol V.F. and hydrocortisone was completed. Lassitude (80 per cent), frontal headache (80 per cent), bodyache (56 per cent), anorexia (64 per cent), abdominal discomfort and gurgling (60 per cent), constipation (56 per cent), diarrhoea (20 per cent), cough 24 per cent), hiccough (4 per cent), semi-consciousness (4 per cent) responded to the combined therapy on the 5·2nd, 4th, 3·5th, 5th, 6th, 6·5th, 4th, 9th, 3rd and 2nd day respectively.

In groups I and II the same line of treatment was followed but apprently the results seem to be better in the latter, because the cases of this group were of moderate severity.

The effect of this line of treatment was seen in the improvement of clinical findings also. Flushed face (seen in 92 per cent), coated tongue with red margins (96 per cent), congested eyes (8 per cent), slow pulse (92 per cent), rapid pulse (8 per cent), tumid and tender abdomen (72 per cent), palpable spleen (80 per cent), enlarged liver (8 per cent), tympantitis (12 per cent) and high temperature 100 per cent) became normal on the 4·5th, 4th, 4th, 5th, 6th, 5th, 7th, 4th, 4th, and 3·5th day of therapy respectively.

During the first week of illness blood culture was positive in 2 out of 7 cases in which culture was made. Culture was negative in cases under therapy during the 2nd and 3rd weeks. Seven cases coming under treatment in the 1st week had

negative Widal reaction, and the five cases who came in the later part of the 1st week had positive agglutination test. Except in one case where the antibiotic was started on the 8th day, the rest of the cases who had begun this therapy in the 2nd and 3rd weeks of their illnesses had positive Widal test. One case came on the 22nd day and had positive agglutination test. Like the cases of group I, the rising titre was not found during this specific antibiotic therapy.

The results of physical findings are comparable to those of symptoms in this group.

Group III—Patients in this group, 18 in number, comprised of cases of moderate severity and were treated with chloramphenicol V.F. alone. Various symptoms like lassitude (77·7 per cent), frontal headache (66·6 per cent), bodyache (55·5 per cent), anorexia (66·6 per cent), abdominal discomfort and gurgling (61·1 per cent), constipation (55·5 per cent), diarrhoea (22·2 per cent), cough (50 per cent), hiccough (5·5 per cent), and semi-consciousness (16·6 per cent) disappeared on 6·5th, 5·2nd, 4·5th, 6·5th, 7·8th, 8th, 5th, 10th, 4th and 3·3rd day of treatment respectively.

The response in the disappearance of various symptoms is slightly slower than in the group II cases in which hydrocortisone was added as an adjuvant.

The effect of this regime of therapy on physical findings was also noted. Flushed face (77·7 per cent), coated tongue with red margin (94·4 per cent), congested eyes (11·1 per cent), slow pulse (88·8 per cent), rapid pulse (11·1 per cent), tender and tumid abdomen (66·6 per cent), palpable spleen (77·7 per cent), enlarged liver (5·5 per cent), tympanitis (16·6 per cent) and high temperature (100 per cent) became normal on the 5th, 5th, 5th, 6th, 7th, 6·5th, 8th, 5th, 4·5th and 4·2nd day of treatment respectively.

As with various symptoms in groups II and III the disappearance of physical findings was seen to be the earlier when hydrocortisone was used in cases of group II than in group III.

Blood culture was positive in one case in this group who came under observation on the 1st day of his illness. The other two cases coming during the 1st week on the 6th and 7th day of their illnesses had negative blood culture. The rest of the cases in this group came during the 2nd, 3rd and 4th weeks of their illnesses and their blood culture was negative. The cases in which the therapy was started in the early part of the first week, the Widal test was negative except in one case in which the titre of *B. typhosus* 'H' 1/250 was found on the 5th day. Two cases which came under treatment in the 2nd week on 8th day had their Widal test negative and in the rest of the patients of this week as also of 3rd and 4th weeks, the Widal test was positive. The rising titre was not seen in this group of cases like the previous ones.

Group IV—This group consisted of 11 cases of enteric fever of moderate severity, very much similar to group II and III. They received treatment with chloramphenicol. Symptoms like lassitude (54·5 per cent), frontal headache (90·9 per cent), bodyache (54·5 per cent), anorexia (72·7 per cent), abdominal discomfort and gurgling (36·4 per cent), constipation (54·5 per cent), diarrhoea (9·1 per cent) and cough (18·2 per cent), disappeared on the 5·5th, 5th, 4th, 5·2nd, 7th, 6th, 3rd and 7th day of the treatment respectively. In this group no patient had hiccough or semi-consciousness or any cerebral symptom. These results were comparable to those of group III. The effect on the amelioration of various positive physical signs were also similar to that of group III. Flushed face (90·9 per cent), coated tongue with red margins (90·9 per cent), congested eyes (18·2 per cent), slow pulse (72·7 per cent), rapid pulse (27·3 per cent), tumid and tender abdomen (36·4 per cent), palpable spleen (63·6 per cent), enlarged liver (9·1 per cent), tympanitis (27·3 per cent) and high temperature (100 per cent) became normal on the 5·6th, 5th, 5th, 6th, 6th, 6th, 7th 4·6th, 4th and 3·5th day respectively.

Of the 3 patients in the 1st week, one who came on the 2nd day of his illness had positive blood culture for *B. typhosus*; the others who came on the 3rd and 7th day had negative blood culture. All of them had negative Widal test. The rest of the patients who came during the 2nd week of illnesses had negative blood culture and positive Widal reaction. The rising titre was not found.

Group V—The 14 cases in this group were of a mild nature. Chloramphenicol V.F. was given in the usual dosage. Symptoms of hiccough, diarrhoea, semi-consciousness, etc., were not present in any patient. Lassitude (42·8 per cent), frontal headache (57·1 per cent), bodyache (42·8 per cent), anorexia (28·6 per cent), abdominal discomfort and gurgling (21·4 per cent), constipation (35·7 per cent), and cough (28·6 per cent) disappeared on the 4th, 4th, 3rd, 5th, 6th, 6th, and 8th day of the treatment respectively.

The symptoms were of a very mild nature and disappeared much earlier than in any of the above groups.

The physical findings in this group were also of a less serious nature and their disappearance was also earlier than in the other groups. Flushed face

(28·6 per cent), coated tongue with red margins (57·1 per cent), congested eyes (10 per cent), tumid and tender abdomen (28·6 per cent), palpable spleen (28·6 per cent), enlarged liver (7·1 per cent), tympanitis (7·1 per cent) and high fever (100 per cent), became normal on the 4th, 4th, 5th, 4·5th, 5·6th, 4th, 3rd and 2·5th day of the treatment respectively.

One case came during the 1st week of his illness with positive blood culture. The rest came during 2nd, 3rd and 4th weeks of their illnesses and had negative blood culture for *Bacillus typhosus*. The Widal test was positive in 5 out of nine cases coming in the second week, and in all the four cases in the 3rd and 4th weeks of their illnesses. The rising titre was not seen in this group also.

The results, in cases of moderate severity (Groups II and III), of treatment with chloramphenicol and with chloramphenicol and hydrocortisone have been compared *vis-a-vis* various symptoms enumerated below and represented in Fig. 1.

1. Cough, 2. Abdominal discomfort and gurgling, 3. Constipation, 4. Lassitude, 5. Anorexia, 6. Frontal headache, 7. Diarrhoea, 8. Bodyache, 9. Hiccough, 10. Semi-consciousness.

There is noticeable difference in the reduction of time factor for the relief of these symptoms when hydrocortisone has been added as an adjuvant (Fig. 1).

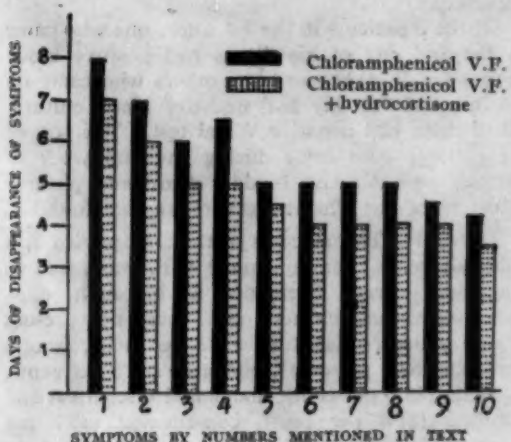
DAYS OF DISAPPEARANCE OF SYMPTOMS
Chloramphenicol V.F.
Chloramphenicol V.F. +hydrocortisone
SYMPTOMS BY NUMBERS MENTIONED IN TEXT

FIG. 1—SHOWING THE EFFECT OF CHLORAMPHENICOL V.F. AND CHLORAMPHENICOL V.F. PLUS HYDROCORTISONE ON VARIOUS SYMPTOMS IN ENTERIC FEVER

The physical findings enumerated below have been represented in Fig. 2:

1. Palpable spleen, 2. Rapid pulse, 3. Slow pulse, 4. Tender and tumid abdomen, 5. Flushed face, 6. Congested eyes, 7. Coated tongue with red margins, 8. Enlarged liver, 9. Tympanitis, 10. High temperature.

There is reduction of time factor in the amelioration of clinical findings when hydrocortisone has been used as an adjuvant (Fig. 2).

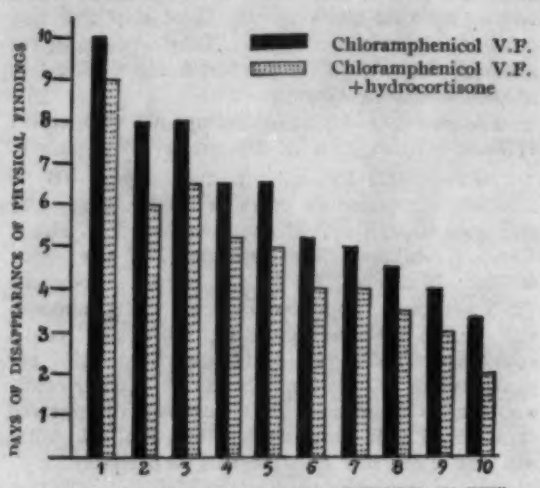
DAYS OF DISAPPEARANCE OF PHYSICAL FINDINGS
Chloramphenicol V.F.
Chloramphenicol V.F. +hydrocortisone
PHYSICAL FINDINGS BY NUMBERS MENTIONED IN TEXT

FIG. 2—SHOWING THE EFFECT OF CHLORAMPHENICOL V.F. AND CHLORAMPHENICOL V.F. PLUS HYDROCORTISONE ON VARIOUS PHYSICAL FINDINGS IN ENTERIC FEVER

Observations were also made on the effect of various lines of treatment upon the complications in these cases. Bronchitis seen in 46 per cent, 32 per cent, 32·2 per cent, 18·2 per cent and 28·6 per cent of cases of groups I, II, III, IV, and V respectively, disappeared on the 12th, 7th, 8th, 7th, and 6th day respectively on different regime of therapy. Pneumonia was seen in one case only in group I which was cured on the 10th day. Circulatory failure was seen in 38·5 per cent of the cases (5 cases) of the severe group, which was controlled on the 6·5th day. Encephalopathy was seen in 3 cases of the severe group and one case of moderate group on chloramphenicol therapy. It disappeared on the 5th and 3rd day of the treatment respectively. *B. coli* infection was seen in 3 cases of group I, one case of group II and one case of group III. The infection was controlled on the 10th to 11th day of the treatment. Hiccough was seen in 2 cases of group I, 1 case of group II, and 1 case of group III. It subsided on the 4th day of the therapy in all groups. Perforation was not seen in any case even in the severe group. Dark coloured stool was seen in 46 per cent, 12 per cent, 22·2 per cent and 9·1 per cent cases of group I, II, III and IV respectively. It was controlled successfully on the

4th, 3·5th, 3·5th and 3rd day of treatment respectively in different groups. Intestinal haemorrhage was seen in case No. 1 of group I, which was seen on the 3rd day and controlled on the 7th day of the treatment.

Relapse—There were 4 patients who came back for treatment of relapse. They belonged to group I (case No. 9), group II (case No. 2) and group III (cases No. 1 and 16). They had received 63, 41, 42 and 52 capsules respectively during their initial attack of enteric fever. They had relapse after 4, 16, 12 and 20 days respectively. They were again given a course of chloramphenicol V.F. and defervescence was noticed after 16, 18, 18 and 16 tablets respectively.

Discussion

Smith *et al* (1949) suggest that the inhibitory effect of chloramphenicol on the esterase system present in bacteria may be concerned in the mechanism of its antibiotic effects. Since it is a naturally occurring analogue of phenylalanine, chloramphenicol might owe its antibacterial properties to interference with the action of phenylalanine and that over a narrow range, more phenylalanine could compensate for the loss of certain reactions inhibited by chloramphenicol. Other workers feel that the antibiotic interferes with the early stage of tryptophane synthesis, specially the formation of indole from anthranilic acid. Chloramphenicol interferes with protein metabolism as indicated by inhibition of glutamate fixation by *Staphylococcus aureus* and glutamyl polypeptide formation by *B. subtilis* (Krantz and Carr, 1958).

Observations in a wide variety of diseases have established that cortisone, ACTH and hydrocortisone exert a suppressive effect on basic processes of inflammation. Hydrocortisone has been found to be the corticoid with the most potent anti-inflammatory activity at the tissue level. Vascular permeability is decreased, exudation diminished and the migration of inflammatory cells impaired with resultant reductions of local phagocytic activity. Thus the classic signs of acute inflammations are lessened and the spread of micro-organisms facilitated. Cortisone and hydrocortisone have been shown to suppress the inflammatory response to a wide variety of agents such as chemical irritants, foreign proteins and micro-organisms. The mode of action of cortisone in inhibiting inflammation remains uncertain inspite of research which has been directed to the elucidation of the problem. There is an evidence to suggest that the inhibition by cortisone of hyaluronidase, an enzyme acting on hyaluronic acid, is at least an important factor in the process. Hyaluronidase increases tissue permeability. A similar increase in permeability occurs in the presence of inflammation and reduction by cortisone may account, in part at any rate, for the anti-inflammatory action of the hormone. In infections, however, the aetiologic agent is not combated and the conditions may become worse inspite of suppression of the outward signs of inflammation, unless specific antibacterial agents are used concomitantly. In enteric fever it has been shown that an even more dramatic clinical improvement can be obtained by giving cortisone as an adjuvant to chloramphenicol therapy. It causes rapid defervescence and lessening of symptoms. So far, as has been determined, this use of cortisone has not been harmful to the patient (Cecil, 1955). In this series of patients receiving treatment with adjuvant hydrocortisone, no untoward reactions were noticed.

Intestinal haemorrhage was seen in one case of group I on the 13th day of his illness. He came under observation for treatment on the 10th day of illness. He had received 15 tablets of chloramphenicol and 4 tablets of hydrocortisone by the time he was having intestinal haemorrhage. As the haemorrhage started in the early stage of therapy it was presumed that this complication was independent of the drugs used. Chloramphenicol and hydrocortisone were continued along with parenteral fluid therapy and haemostatics like vitamin C, vitamin K, and coagulan. Analeptics like pholedrine, percorten and coramine were added to combat the ensuing circulatory failure with good results.

It is remarkable that on hydrocortisone therapy in group II cases there was a dramatic improvement on the third day and the temperature came down to normal (3·5 days). Similar patients in group III who were treated with chloramphenicol only took one day more (4·2 days) for defervescence. This defervescence may be attributed to the anti-inflammatory properties of hydrocortisone. The average number of tablets required for defervesence of cases in group II was 18·5 ; as compared to this, in group III 21·5 tablets were used. The defervescence period in cases of groups I, IV and V was 4·8, 3·4 and 2·5 days respectively. The average number of tablets needed for defervescence in groups, I, IV and V was 26, 20·4 and 16 respectively. While treating the relapse cases, defervescence period was 2·75 days and on an average 16 tablets of chloramphenicol were required. This period of defervescence and the amount of chloramphenicol needed were lesser than those in the case of initial attack.

SUMMARY

Eighty-one cases of enteric fever were treated with chloramphenicol, with and without hydrocortisone, and 13 severe cases with chloramphenicol V.F. and hydrocortisone. Twenty-five moderate cases received chloramphenicol V.F. and hydrocortisone while twenty-nine moderate cases had chloramphenicol only. Fourteen mild cases had chloramphenicol only.

The defervescence period was cut down by one day when hydrocortisone was used as an adjuvant along with chloramphenicol in the treatment of enteric fever. The average number of tablets needed for defervescence was 18·5 when hydrocortisone was used. The average daily dose given was 6 tablets (1·5 g.) in divided doses.

Symptoms and physical findings disappeared earlier when hydrocortisone was also used with chloramphenicol.

Side-effects were minimal. Nausea and vomiting were noted in a few cases.

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SPECIAL ARTICLE

THE ENTEROVIRUSES

(A Review)

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A large number of viruses, capable of producing human disease, have been isolated from the gastro-intestinal tract and faeces. The poliomyelitis, Coxsackie and ECHO viruses, the hepatitis viruses, the adenoviruses, and herpes simplex virus, and many other ill-defined agents are already known. Of these heterogenous viruses, poliomyelitis, Coxsackie and ECHO viruses constitute a closely related group and they have been called the enteroviruses (Committee, 1957).

HISTORICAL

Of the enteroviruses, poliomyelitis was the first virus to be discovered in 1908 (Landsteiner and Popper, 1908). At that time, however, it was far from being an 'enteric virus'. The isolation from nervous tissue was carried out by intracerebral inoculation of monkeys and until lately it was considered to be a 'neurotropic' virus. Isolations of the virus from faeces was reported as early as 1911 (Kling et al., 1911) but it was not until 1937 that Harmon (1937) established its presence in the stools and Sabin and Ward (1941) isolated it from different parts of the intestinal tract, the walls of the ileum and the colon. Since then, a number of workers have confirmed the presence of virus in oropharynx and the gastro-intestinal tract. Melnick (1947) calculated that 100 g. of stool may contain 1000 to 10,000 monkey infective doses of the virus.

During nineteen thirtees, two other 'Polio viruses' were discovered. Theiler (1934, 1937) isolated the virus of mouse encephalomyelitis and Klobouk (1933) described the virus of Teschen disease of pigs which had been known to occur in Czechoslovakia since 1929. Gard (1943), on the basis of clinical picture in the respective hosts, pathology, epidemiology, and other properties of these viruses, called them the "poliomyelitis group of viruses" and suggested the use of the term human, murine, and porcine types of poliomyelitis virus.

This view of a group of 'polio' viruses was, however, not accepted by some workers (Committee, 1948), while others continued to hold the previous position (Gard. 1949 ; Jungeblut, 1950). Von Magnus *et al* (1955) proposed the term 'poliovirus' with the suffixes 'hominis' and 'muris' for the human polio and Theiler's virus respectively. It may be noted that both the viruses are found in the alimentary tract, faeces and nervous system of their natural hosts and both are transmitted through oropharyngeal secretions or faeces.

The use of monkeys as the only susceptible laboratory animal in polio studies presented many difficulties. Attempts were, therefore, continually made to adapt the virus to laboratory rodents (Armstrong, 1939). The Coxsackie viruses were

discovered during the course of attempts to isolate the polio viruses in infant mice (Dalldorf and Sickles, 1948). From the stools of two children, a virus was isolated which induced paralysis in suckling mice and hamsters but not in monkeys. The paralysis was found to be due to widespread damage to the skeletal muscles with apparently little damage to the central nervous system. In 1949, Dalldorf isolated another 10 strains and noted that they were not similar antigenically. Coxsackie viruses have now been isolated from many parts of the world (Wilson and Miles, 1955 ; Parrott, 1957) and numerous disease syndromes are known to be associated with them (Dalldorf, 1955 ; Sprunt, 1957).

After the discovery by Enders *et al* (1949) that polio virus could grow and produce cytopathogenic change on non-nervous tissue of primate origin, tissue culture became a standard tool for the growth and study of polio viruses. The introduction of this new technique soon presented fresh problems. Cytopathogenic agents other than poliomyelitis viruses were detected (Robbins *et al*, 1951 ; Riordan *et al*, 1952 ; Melnick and Agren, 1952 ; Steigman *et al*, 1953 ; Hammon *et al*, 1957). Similar viruses were discovered not only from suspected cases of polio infection but also from faeces of healthy children (Ramos-Alvarez and Sabin, 1954). Their pathogenicity was ill-understood and Duran-Reynals (Committee, 1955) suggested that they be called 'orphan' viruses in search of disease. Very soon these viruses were pooled, renamed ECHO viruses (Enteric Cytopathogenic Human Orphan Viruses). The Committee for ECHO viruses (1955) defined them as viruses which were cytopathogenic to monkey kidney cell cultures, were neutralised by gamma globulin, were not neutralised by polio and Coxsackie anti-sera and were not related to any of the known viruses found in human gastrointestinal tract. A redefinition of the poliomyelitis, Coxsackie and ECHO viruses, however, became necessary in 1957 (Committee, 1957).

Morphology of Enteroviruses

All three groups of enteroviruses are of relatively small size. According to von Magnus *et al* (1955), poliomyelitis virus is roughly spherical with a diameter of 25-32 μ as shown by filtration and sedimentation experiments. Under the electron microscope, the virus was found to have a size of 28 μ (Bachrach and Schwerdt, 1954). Benyesh *et al* (1958) estimated the size of poliomyelitis viruses by ionising radiations and found it to be 24 to 32 μ. The size of the complement fixing antigen was, however, between 7-13 μ. Alexander *et al* (1958) could separate the RNA of the virus particle and the HeLa cells in tissue culture could be infected by RNA alone.

The size of the Coxsackie viruses has been found to be more variable. They are also spherical but their estimated diameter varies from 7 to 35 μ (most of them being 25-30 μ) according to the strain examined and the method used (Melnick *et al*, 1951 ; Wilson and Miles, 1955).

Ultrafiltration experiments showed that the ECHO viruses, types 1, 2, 3 had a diameter of 11-17 μ. ECHO 10, however, was found to have a size of 60-90 μ (Committee, 1955). More recently ECHO 7 was found to have a diameter of 30 μ and ECHO 1 had a diameter of 43 μ with ionising radiations (Benyesh *et al*, 1958 ; Melnick, 1957).

Resistance to Physical Agents

(*a*) *Heat*—Human faecal poliomyelitis virus in water was inactivated between 50°-55°C, when heated for 30 minutes. Milk or milk products exerted a protective effect. Lansing and Y-SK strains of polio-2 virus, differ in their thermolability ; Lansing strain in milk was inactivated at 50°C in 30 minutes while the Y-SK strain was not.

Coxsackie viruses in mouse brain suspension are killed at 55°C in 30 minutes (Robinson, 1950). Milk and dairy products were found to protect although pasteurisation destroyed them (Kaplan and Melnick, 1954).

(*b*) *Light, U-V ray, etc.*—Polio virus is rapidly killed by ultraviolet light. It resists x-rays and sonic vibrations. It survives in water for a month in light and for 3-4 months in the dark (Wilson and Miles, 1955). Drying inactivates the polio virus quickly but residual traces of moisture favours its survival (Faber *et al*, 1951). U-V ray was found to inactive Coxsackie viruses (see Dalldorf, 1955).

(*c*) *Freezing, etc.*—Polio virus survives ice box temperature for several months and could be stored at −70°C for an indefinite period (Howe, 1952).

Coxsackie virus could also be stored frozen at −20°C or −70°C for long periods (Melnick, 1951). Positive ECHO virus isolations could be obtained from stools stored at −20°C (Honig *et al*, 1956). ECHO type—19, however, could only be preserved at −70°C (Melnick and Sabin, 1958). At 4°C, ECHO-7, 8 and 11 in high concentrations did not lose activity for 3-4 weeks but ECHO 9 and 10 gradually lost their titre.

Resistance to Chemical Agents

All the three groups of viruses are resistant to ether (Committee, 1957). They are equally resis-

tant to the antibiotics commonly used against bacterial and mycotic infections. Glycerol, likewise preserves them. Polio viruses could stay upto 15 months (Gharpure, 1951) in 50 per cent glycerol at 4°C and even upto 4-6 years (Wilson and Miles, 1955), while Coxsackie viruses in 50 per cent glycerol have been known to survive for 70 days at room temperature and in ice box for over one year (Melnick & Ledinko, 1950).

Chlorine has a marked virucidal action on these viruses. Polio virus is said to be destroyed by 0·05 p.p.m. of free chlorine in 10 minutes (Lensen *et al*, 1947). The Coxsackie viruses are killed by 0·6 p.p.m. of chlorine at pH 7 in 10 minutes (Clarke and Kabler, 1954).

Lysol has little action on polio and Coxsackie viruses. Stanley *et al* (1953) found some strains of Coxsackie viruses which were sensitive to the action of lysol. Formaldehyde inactivates polio viruses which may acquire the property of delayed infectivity (Gard, 1957).

Susceptibility of Laboratory Animals to Enteroviruses

Enteroviruses produce clinical disease in monkeys and infant mice but do not propagate readily in other laboratory animals although some strains have been adapted to cotton rats and chick embryos as well.

(*a*) *Monkeys*—The monkey has been one of the commonest laboratory animals used for the study of polio viruses. A large number of species of simians have been found to be as susceptible to polio viruses as the rhesus; of the numerous routes attempted the intracerebral route has been most successful in securing experimental infection.

After an average incubation period of 7-10 days, the animals come down with paralytic disease. Increased proteins and cells in C.S.F. in the absence of clinical disease have been recorded (Gharpure and Swaminathan 1952). Non-paralytic attacks followed by recovery, may occur. Virus can be recovered from different parts of the brain and the cord, from nasopharynx, lymph nodes, intestinal tract and the faeces. Histologically, diffuse involvement of the brain and the spinal cord is found characterised by neuronal destruction, inflammatory cells and gliosis (Gharpure, 1950, 1952). Intranuclear inclusions, in surviving neurones, have been described (Howe, 1952).

Coxsackie viruses were not found to be pathogenic to monkeys, but were known to produce subclinical infection (Melnick and Ledinko, 1950a). Oral administration of Ohio I strain of Coxsackie virus to cynomolgus (not rhesus or cercopithecus) monkeys resulted in pyrexia for a brief period. The virus was excreted in faeces for a few days and neutralising and complement fixing antibodies were found to develop.

Chimpanzees could also be infected by the oral route (see Melnick and Curnen, 1952), to produce an inapparent infection. Viraemia was followed by a pharyngeal-intestinal carrier state and neutralising antibodies appeared. Reinfection with the same virus was not possible so long as these antibodies were present.

More recently, Coxsackie viruses have been found to produce lesions in monkeys. Steigman (1957) refers to a virus which was isolated by inoculating stools into rhesus monkey in 1949. The distribution of lesions was typical of a polio virus. The nervous tissues of the monkey had been preserved and later, *in vitro* studies, revealed only Coxsackie B-2.

In 1952, Russian workers isolated a virus from a case of bulbar polio which produced typical polio-like lesions in monkeys (Chumakov *et al*, 1956). The Russian workers named it as polio type 4 but other workers on investigation found it to be Coxsackie A-7 (Habel and Loomis, 1957; Johnsson and Lundmark, 1957; Horstmann and Manuelidis, 1958). Other strains of Coxsackie A-7 and A-14 also produce similar lesions in monkeys (Dalldorf, 1957b).

Some ECHO viruses (type 4 and 6) produced inapparent infection in chimpanzees (Itoh and Melnick, 1957). The viruses were excreted in throat and stools and complement fixing and neutralising antibodies could be demonstrated. Wenner and Chin (1957) found focal lesions in the lumbar and cervical segments of the cord of occasional monkeys when ECHO types 1, 2, 3, 4, 6, 10 and 13 were given intramuscularly. Neuronal damage, glial proliferation and mononuclear infiltration was seen. Inoculated intraspinally or intracerebrally ECHO types 7 and 8 were found to produce focal intestitial infiltration in the gray matter of medulla and midbrain (Ramos-Alvarez and Sabin, 1954). ECHO-17 produced polio-like neuromal destruction and infiltration of spinal cord. ECHO-10 produced destructive lesions of ventricular ependyma and choroid plexus (Melnick and Sabin, 1958).

(b) *Laboratory rodents*—Polio virus (Lansing strain) was adapted to cotton rats and is known to produce typical lesions of polio-encephalitis (Armstrong, 1939; see van Rooyen and Rhodes, 1948).

Mice have been infected with Lansing strains of polio virus, which had passed through cotton rats. Following intracerebral inoculation, ence-

phalitis and flaccid paralysis were seen. The newborn mice were, however, resistant to infection by Lansing strain. Casals et al (1951) adapted, by rapid serial passages, the MEF strain of Lansing polio to infant mice. Li and Habel (1951) reported the adaptation of Leon (Polio type 3) strain to mice by the intraspinal route. Later type 1 polio virus was also adapted to mice (Li and Schaeffer, 1953).

Stanley and Dorman (1953) reported a polio virus (isolated from brain and spinal cord of a child) which was pathogenic for suckling mice and monkeys but not for adult mice. In the infant mice, lesions were quite unlike those produced by Coxsackie viruses, Selzer (1957) reported the adaptation of polio type 1 (Mahoney strain) to suckling mice. This strain had been previously adapted to adult mice by repeated intraspinal and later intracerebral inoculations. The virus in infant mice showed two cycles of multiplication. The first occurred 48 hours after inoculation and was not associated with paralysis ; the second occurred when mice were 10-14 days old and was associated with paralysis of limbs.

Cortisone has been used to enhance the lesions of experimental poliomyelitis in new born hamsters. Following cortisone treatment, viraemia was enhanced due to growth of virus in skeletal muscles which showed changes simulating those produced by Coxsackie viruses (Aronson and Shwartzman, 1953). The same authors (1956) showed that polio type 2 also grew in brown fat of cortisone-treated hamsters producing changes, very similar to those produced by Coxsackie B viruses.

The Coxsackie viruses produce a variety of lesions in mice (Pappenheimer et al, 1950 ; Gifford and Dalldorf, 1951 ; Melnick and Curnen, 1952). In inoculated infant mice, signs of disease appeared in 2-10 days with paralysis of extremities. With other strains, tremors and spasticity of the limbs were observed. Mice were susceptible mainly through the parenteral route (Kaplan and Melnick, 1951) and they become markedly resistant, with advancing age. Gifford and Dalldorf (1951) found that Group A strains produce hyaline degeneration followed by active repair of the striated muscles of limbs, diaphragm, thorax, abdomen and those of throat, jaw and scalp. Group B strains of Coxsackie viruses, however, show only patchy involvement of skeletal muscles particularly of the psoas, masseter and the tongue muscles. Visceral lesions and involvement of the central nervous system is however, more common. Brain shows widespread neuronal death and, in surviving animals, cystic spaces form as a result of liquefaction of the brain substance. Necrotising steatitis of the peripheral parts of the foetal fat lobules is also commonly seen. Myocarditis was observed in about 6 per cent animals with hydropic degeneration and collection of funchsinophilic granules. Banker (1954) also noted lesions of myocardium in a certain proportion of mice. Hepatitis and pancreatitis occurred in a small proportion of animals inoculated with group B Coxsackie viruses. Albrecht and Mayer (1958) found that Coxsackie B strains also produced parotitis in suckling mice. Pappenheimer *et al*, (1951) noted that in older animals, pancreatitis was the only lesion observed.

Coxsackie A-14, however, was found to produce polio-like lesions in adult mice (Dalldorf, 1957b) and it was suggested that age of the animals seemed to determine the development of the experimental lesion. In the newborn, only muscle lesion was produced ; in older animals, only polio type lesions were produced while at the age of 10-14 days both types of lesions were seen. Dalldorf (1952) also suggested that the neuraxis may be susceptible, but the young mice die before the lesion could develop.

The effect of age on the susceptibility of infant mice was thought to be due to involuting adrenals (Dalldorf, 1955) and administration of cortisone to adult mice restored the susceptibility. On the other hand, Walker and Boring (1958) found that Coxsackie B-1 when inoculated into adult mice kept at 4°C, was fatal in 3-6 days with lesions in the heart, liver and intestines. At 25°C, only pancreatitis was produced. This loss of resistance at 4°C, was, however, not solely due to adrenocortical hypersecretion because ACTH did not have the same action.

Dalldorf (1951) found that infant mice were rendered very resistant to polio virus if they had been infected with a Coxsackie B virus 8-10 days earlier.

Sulkin *et al* (1953) found that polio and Coxsackie viruses, when inoculated together into mice, influenced the experimental disease. Given simultaneously into 4 weeks old mice, the virulence of Coxsackie virus (Ohio strain) was found to be enhanced. Nancy strain, however, remained unaffected but altered the course of Lansing Polio given simultaneously.

ECHO viruses were at first found to be non-pathogenic to mice. ECHO-9 and 10 strains, however, after passage in tissue culture, have been found to produce lesions in infant mice resembling Coxsackie A and B respectively (Committee, 1957). Some strains of Coxsackie B virus also, on primary isolation were non-pathogenic to mice and thus behave like ECHO viruses.

(c) *Chick embryo*—Poliomyelitis viruses have been adapted to grow on the chick embryo. The SK and Lansing strains were propagated by the chorio-allantoic and yolk-sac routes and invaded viscera (Schultz and Enright, 1946). Polio virus type-2 has been adapted to chick embryo after passage through hamsters (Roca-Garcia *et al*, 1952 ; Cabasso *et al*, 1952). One strain of Coxsackie viruses had been adapted to developing chick embryo (Huebner *et al*, 1950). Among the ECHO viruses, type 10 was found to grow in chick embryos (Dalldorf, 1957a).

Growth of Enteroviruses in Tissue Culture

Reports of the growth of polio virus in tissue culture, had appeared periodically since 1913 ; but it was not until 1949, that Enders *et al* (1949) put the growth of poliovirus in suspended primate tissue cultures on a sound footing. Using cell cultures obtained from human embryonic skin, muscle, intestine and nervous tissues, they showed degenerative changes which were attributable to the virus. A correlation between virus growth and cytopathogenic effect was also established.

During last ten years, a number of other advances have been made in the use of tissue culture methods for the study of polio and related viruses. Cells can now be grown in monolayers on glass surfaces and stationary tubes can be used instead of revolving drums and special chambers for carbon dioxide. The growth media have been refined and simplified (see Melnick, 1953 ; Enders, 1954 and Ross and Syverton, 1957). The use of kidney epithelial cells from humans, monkeys and other animals and trypsinisation procedures have made those techniques universal (Rappaport, 1956). A number of internationally recognised continuous cell lines have been developed from normal human or animal tissues by transformation or by cultivating malignant cells obtained after surgical procedures (Ross and Syverton, 1957).

Behaviour of enteroviruses in some of the most commonly used tissue cultures :

(a) *Monkey kidney tissue culture (MKTC)*—Polio viruses grow very well and produce a marked and rapidly developing cytopathogenic effect in the monolayer cells, which can be observed under the microscope (Melnick, 1953).

The Coxsackie viruses generally do not grow in MKTC except for B-1 through B-5 strains (Sickles *et al*, 1955a). Coxsackie A-9 was reported to have been isolated in MKTC, (Sickles *et al*, 1955b).

All the ECHO viruses grow in MKTC, which is considered to be the most sensitive culture for isolating them (Committee, 1955). Hsiung and Melnick (1957b) found that different species of monkey kidney tissue cultures showed differential susceptibility to enteroviruses. Thirteen species of monkeys and 4 species of baboons were tested and 6 of them were found to be as sensitive as the rhesus monkey. The African red grass monkey (*Patas*) kidney cells were found to be twice as susceptible to polio, Coxsackie B and ECHO-7, 8 and 12 viruses. It was however, resistant to Coxsackie A-9 and ECHO-1, 3, 4, 6, 9 and 14. MKTC from two other African species showed even greater susceptibility to all the three groups of viruses. Baboon cells were similar to rhesus for polio viruses but Coxsackie A-9 and ECHO-1 did not produce any cytopathogenic effect in cells from one species. The failure to produce cytopathogenic effect (CPE) on *patas* cells was not due to failure of absorption as was the case when polio virus failed to grow on MKTC from *capuchin* monkey of South America. Coxsackie A-9 and ECHO-1, did multiply on *patas* cells to a limited extent but only when heavy inocula were used (10^7) and this resembled the growth of attenuated polio virus on low bicarbonate medium (Hsiung and Melnick, 1958a). Ormsbee and Melnick (1957) found that *capuchin* monkey cells supported the growth of ECHO-10 while *patas* and *cercopithecus* allowed ECHO-7, 8 and 12 to grow. The comparative susceptibility of kidney cultures from primates and a number of other animals to ECHO viruses was tested by Hsiung (1958) who found that ECHO type 10 showed distinctive growth characters which could differentiate it from other ECHO viruses.

(*b*) *HeLa cells (cell line derived from human carcinoma)*—Polio viruses grow easily on HeLa cells and produce a typical cytopathogenic effect (Scherer *et al*, 1953).

Coxsackie viruses A-11, 13, 15 and 18 grew and produced CPE on HeLa cells while Coxsackie A-9 did not have any effect. Among the B strains, B-2 and B-4 had a limited action on these cells (Sickles *et al*, 1955b ; Ormsbee and Melnick, 1957). The latter workers also tested the ECHO viruses on HeLa cells and found that only some of them (ECHO types 5, 6, 8, 11, 12 and 13) could produce a detectable, specific cytopathologic effect on cellsheet. Some ECHO (2 and 7) viruses were found by them to produce considerable multiplication on HeLa cells with minimum cytopathologic change. Stulberg *et al* (1958) found that the HeLa cells were susceptible to ECHO-1, 3, 6, 7, 8 and possibly 10 and 12 as well. Archetti *et al* (1957) found that except for ECHO-4, all ECHO prototypes could be grown on HeLa cells. CPE was seen on 3rd-5th day and only 70-90 per cent cells were destroyed with a virus yield of 10^4-$10^{7.5}$ $TCID_{50}$/ml.

(*c*) *Detroit cell lines*—Two types of cell lines derived from human sources were developed by Henle and Deinhardt (1957). One series resembled epithelial like cells (Ep-L) and the other looked like fibroblasts (Fb-L). Both were found to support the growth of polio and Coxsackie viruses and this was associated with cytopathogenic effect. Stulberg *et al* (1958) studied the comparative behaviour of 16 ECHO virus types in Ep-L and Fb-L cell lines. All of them, except ECHO-10 multiplied in Fb-L cells. CPE was produced in 1-3 days. ECHO types 7 and 11 produced changes rapidly while type 15 was definitely slower. Ep-L strains were much less susceptible and only ECHO 6 and 10 grew on them, CPE was difficult to determine in these cells.

(*d*) *Human amnion*—Human amnion cell cultures are comparatively of recent origin (Weinstein *et al*, 1956; Lahelle, 1956; Dunnebecke and Zitcer, 1957; Becker *et al*, 1958 and Ferguson and Tobin, 1958). Weinstein *et al* (1956) found polio virus to grow well and also produce a cytopathogenic change. Coxsackie A-9 and B-3 were similar but B-2 and B-4 did not grow. Human amnion cells could detect some ECHO-9 strains (Quersin-Thiry *et al*, 1957) while other strains had no effect (Faulkner *et al*, 1957). Similarly ECHO-18 could not be detected (Eichenwald *et al*, 1958) and ECHO-16 did not show a typical CPE (Neva and Zuffante, 1957).

Lane and Marshall (1957) isolated 65 polio and 8 ECHO viruses from 280 specimens on amnion cultures.

The effect of these viruses on numerous other cell cultures is reviewed by Enders (1954) and Ross and Syverton (1957).

(*e*) *Nature of the cytopathogenic changes*—In primary isolation, polio viruses may grow rapidly and produce a widespread CPE in the cell sheet in 48-72 hours (Kirby and Evans, 1955), while Coxsackie and ECHO viruses usually grow slowly and produce focal degeneration and a generalised effect in 7-10 days. Attenuated strains of polio, however, may lead to a restriction or delay in the formation of plaques particularly in a low bicarbonate medium (Vogt *et al*, 1957; Hsiung and Melnick, 1958b).

The type of changes produced in the MKTC or HeLa cells can be of help to differentiate the three groups of viruses (Melnick 1957). Harding *et al* (1956) found that in HeLa cells infected with polio virus, cytological alteration could be detected as early as 6 hours after infection. Formation of cytoplasmic mass, distortion of the nucleus and its shifting towards the periphery, general contraction of the cell with its rounding up and formation of cytoplasmic projections, was invariably associated with infection. Reissig *et al* (1956) described similar changes and classified them into 8 types of cells undergoing gradual alteration in appearances. The evidence for a 'toxin' responsible for cellular damage has recently been shown by Ackerman *et al* (1958).

Bernkopf and Rosin (1957) found that Coxsackie A-9 and B-3 produced changes different from those of polio. The cells were rounded up early and there was a sharp separation of ectoplasm and endoplasm, and the protoplasmic processes were straight as seen in stained preparations. The cells infected with ECHO viruses (types 1, 3, 5, 6 and 7) retained a polygonal or triangular shape and normal cells were seen simultaneously along with severely damaged cells. Shaver *et al* (1958), however, found that the cytologic effects of polio, Coxsackie and ECHO viruses in monkey kidney tissue cultures revealed a remarkable similarity. Only ECHO-10 changes differed significantly.

(*f*) *Plaque morphology with enteroviruses*—Formation of localised areas of viral CPE on a monolayer of tissue culture with polio virus with agar overlay was introduced by Dulbecco and Vogt (1954). Hsiung and Melnick (1955) studied the morphology of the plaques on bottle culture of MKTC. Plaques were visible to the naked eye and the morphology of polio and Coxsackie A-9 was found to be similar; round plaques appeared in 2-3 days with well defined margins. Coxsackie B-2 and B-5 produced plaques with indistinct boundaries. Coxsackie B-3 and B-4 produced plaques earlier than B-2 and B-5 and resembled polio plaques more closely.

With ECHO viruses, the formation of plaques was delayed for 5-6 days. For next 2-3 days, they were found to increase in size but not in number. Some strains required 12-13 days for the plaques to become manifest. The boundaries of these plaques were irregular and diffuse and healthy cells could be seen in areas of degeneration.

Hsiung and Melnick (1957a) in a more detailed study with rhesus monkey kidney cells found that ECHO-7, 8 and 12 produced plaques resembling those of polio viruses. Types 1 and 13 produced plaques with diffuse edges with a clear centre. Types 3, 4, 6, 9 and 14 produced irregular plaques with a hazy centre. ECHO-2, 3, 5, 6 and 10 did not produce plaques.

Antigenic Structure of Enteroviruses

(*a*) *Polio viruses*—The occurrence in nature of different immunological types of polio virus was first suggested by Burnet and Macnamara (1931). Several subsequent workers using cross neutralisa-

tion tests reached similar conclusions. Bodian *et al* (1949) established three distinct serological types, type 1—Brunhilde, type 2—Lansing and type 3—Leon. A detailed report on classification of 100 strains was published in 1951 (Committee, 1951). Tests carried out *in vivo* in monkeys and *in vitro* in tissue culture, did not show any cross protection or cross neutralization between these three types.

This antigenic classification of polio viruses is, however, not wholly supported by complement fixation tests. Although, type specific antibodies can be shown, heterologus cross reactions, due to group antigen, also occur (Black, 1955 ; Melnick, 1957).

Polio viruses are antigenic and produce neutralising antibodies which are responsible for protection (Melnick, 1953). Neutralising antibodies can be produced both by oral and intramuscular route and persist for years. Intratype differences in antigenicity are known ; Lansing and Y-SK (both polio-2) differ in their capacity to produce antibodies in cyanomolgus monkeys. Freund's adjuvants have been found to increase the antigenicity of the virus vaccines (Salk *et al*, 1951).

Serologically the polio viruses react with their antibodies in a number of ways of which neutralisation and complement fixation have already been mentioned. According to Melnick (1957), complement fixing antibodies against the group antigen were formed rapidly and reached their highest titre quickly. Complement fixing type specific antibodies were associated with live virus and appeared in the third week of disease and were generally not seen in the absence of neutralising antibodies. Inactivation by heat, UVR or formalin uncovers a marked group reactive antigen which is common to all the three immunological types. With heated antigens, sera may show heterologous complement fixing antibodies without neutralising antibodies.

Neutralising antibodies of different avidities appear at different times after natural infection, experimental infection with attenuated strains and after formalinised vaccine (Sabin, 1956). Antibodies of low avidity, best shown by pH test, appear first and its titre can be more than 60 times higher than antibody of high avidity demonstrated by CPE test in tissue culture. Persons with subclinical infection may only show low avidity antibody and the same was true of volunteers infected with attenuated srains.

Flocculation reaction has also been studied with purified polio virus preparation. Smith *et al* (1956) described a micromethod which gave good results for typing purposes. Grasset *et al* (1958) have described a rapid slide precipitin microreaction with poliomyelitis antigens and antisera in agar. These tests, however, are still in experimental stages.

A haemagglutination test for titration of antibodies to polio viruses has been described with virus absorbed or tanninised sheep red cells used as antigen (McKenna *et al*, 1958). Twelve per cent sera gave antigenic cross reactions with this test and an over all all correlation of 57 per cent with neutralisation tests was observed.

Polio virus *hominis* so far has not been found to cause viral haemagglutination. Swaminathan (1954) used red cell suspensions from 9 animals and tested them with monkey cord suspensions as a source of virus but without any positive results.

(*b*) *Coxsackie viruses*—On histological grounds Coxsackie viruses were divided broadly into two groups—A and B (Dalldorf, 1950). They seem to differ in some other properties as well (Tobin, 1953). The differentiation is not always so clear cut (Godman *et al*, 1952). Stanley *et al* (1953) described a third group C which only caused encephalitis in suckling mice.

Serologically, the Coxsackie viruses were found to be heterogenous and type numbers have been used to designate the serological varieties in each group. Ten types (1-10) were first described in Group A and three (1-3) in Group B Coxsackie viruses (Dalldorf, 1952). Since then 9 more Coxsackie A and 2 Coxsackie B viruses have been added bringing the total to 24 serological types of Coxsackie viruses (1-19 of Group A and 1-5 of group B (Committee, 1957).

The Coxsackie viruses are antigenic and produce both neutralising and complement fixing antibodies in human beings and animals (Melnick and Curnen, 1952). Suspensions prepared from muscles of infected baby mice can be used as antigens for producing neutralising antibodies in adult mice or other animals. Antigens for complement fixation tests could be prepared from infected tissues or from tissue culture fluid. Nonspecific rise in antibodies against heterologus types was, however, found both in chimpanzees and human beings. The results of complement fixation tests, therefore, may be misleading. In tissue culture, particularly with Coxsackie B, a fraction of the virus particles seems to resist neutralisation in tube cultures even in the presence of serum. In such instances, the plaque reduction method has been used to provide a definite answer. Plaque reduction of 80 per cent or more identifies the virus (Melnick, 1957).

Rogers *et al* (1958) has devised a metabolic inhibition test based on pH changes for determination of antibodies to group B Coxsackie viruses.

A colorimetric method (Schmidt *et al*, 1958) useful for Group B viruses and for tissue culture growing Group A viruses, has also been described.

Viral haemagglutination with Coxsackie viruses was not known to occur but Goldfield *et al* (1957) has recently described weak haemagglutinating activity with Group B viruses using human O-group cells.

Numerous attempts have been made to study the mutual effects between Coxsackie and polio viruses. In monkeys, no evidence of interference between the polio and Coxsackie A viruses could be obtained (Howitt and Nichols, 1952). Some evidence of interference between polio and Coxsackie B viruses was recorded by other workers in mice. It was shown that Group B viruses modified the course of experimental poliomyelitis in mice (Dalldorf, 1951) and tissue culture (Le Bouvier, 1954). Recently Dalldorf and Weigand (1958) noted that paralytic poliomyelitis could be produced as a result of combined action of attenuated polio virus and Coxsackie A-14 virus ; neither of which could produce the paralysis by itself. Among human populations, some investigators suggested that during period of prevalence of Coxsackie B virus infections, cases of poliomyelitis did not occur. But both viruses have been isolated from the same patients a number of times (Dalldorf, 1955 and Melnick and Curnen, 1952).

(c) *ECHO viruses*—ECHO viruses have been found to be serologically heterogenous. In 1955, a total of 13 (ECHO 1-13) ECHO strains were defined. Type 1 had been obtained from Egypt. Types 2-11 had been pooled from different parts of U.S.A. and types 12 and 13 had been obtained from Philippines. Types 1 and 7-13 had been obtained from stools of healthy children while types 2-6 had been obtained from stools of cases of aseptic meningitis.

All the thirteen prototype strains had been grown in MKTC (Committee, 1955). Since this report, 6 more ECHO types have been recognised and confirmed (Committee, 1957). All the prototype strains had been obtained from different towns in U.S.A. Types 14 and 16 were isolated from cases of aseptic meningitis, types 15 and 17 from healthy individuals and types 18 and 19 from cases of diarrhoea. Five new strains are under discussion. Type 20 strains were recovered from an outbreak of febrile illness (Rosen *et al*, 1958) ; type 21 from aseptic meningitis and types 22, 23, 24 from cases of diarrhoea (Melnick and Sabin, 1958).

Cross relationship between some ECHO viruses has been discovered. Types 1 and 8 neutralised each other up to a high titre. This cross reaction was present even when the viruses had been plaque purified (Committee, 1957). One way cross-reactions between ECHO types 12 and 8, and 12 and 1 have also been seen (type 12 antiserum neutralises type 8 and type 1 viruses and not *vice versa*) (Committee, 1957). ECHO antisera (1-14) with the exception of 3 and 6 failed to neutralise 3 types of polio virus, 10 adenoviruses, Coxsackie B-1 to B-5 and A-9. Some cross reactions between ECHO type 2 serum pool and Coxsackie A-9 were observed and ECHO 6 anti-serum had a titre of 1/64 against Coxsackie B-3 (Committee, 1957). The cross reactions produced by type 13 were found to be due to a mixture of ECHO-1 and 13. Plaque purified virus eliminated them. Within ECHO virus types, strains of broader antigenicity have been found to exist and these have been called 'prime' strains. 'Prime' strain antisera have been found to neutralise other prototype strains but these themselves are not effectively neutralised by prototype sera. 'Prime' strains are now known to be present among strains belonging to ECHO types 5, 6, 7, 9, 10, 11 and 13 (Committee, 1957).

Antigenic relationship between ECHO-9 and herpes simplex virus has been shown (Krech, 1957). Tyrrell *et al* (1958) have described an ECHO virus related to ECHO-9 but sharing some antigens with Coxsackie A-9. Infection with ECHO-6 has been known to produce antibodies against heat inactivated antigens of polio viruses (von Zeipel and Svedmyr, 1957).

ECHO viruses are antigenic and produce neutralising, complement fixing (Committee, 1955) and haemagglutination-inhibiting antibodies (Lahelle, 1958). The neutralisation tests have been carried out in MKTC tubes. Some ECHO sera have been found to be poor antibody producers as ECHO-4 but by plaque reduction, the titre of this serum too was found to be quite high (Committee, 1957).

Tissue culture fluid can be used as antigen for complement fixation. Fluorocarbon purified tissue culture fluid antigens have been tested for complement fixation tests (Halonen *et al.*, 1958a, 1958b). Two way cross reactions were seen between ECHO types, 1, 8 and 13 and one way cross with type 13 antigen and type 12 antiserum was also noted. A lack of correlation between infectivity titre and antigen titre was also noted. Guineapig sera also showed a lack of correlation between titres of complement fixing and neutralising antibodies.

Haemagglutination by some of the ECHO viruses has been described (Goldfield *et al*, 1957 ; Lahelle, 1958). Goldfield *et al* (1957) found that

MKTC fluid containing ECHO—3, 4, 6, 7, 10, 11 and 12 caused agglutination of human 0-group cells. Elution of the virus was also noted. The property was found to be due to the virus particle and haemagglutination inhibition tests were possible.

Lahelle (1958) found that some strains of ECHO 6 grown in human amnion (not D' Amouri-the prototype strain) caused agglutination of human 0-group cells at pH 7·0. Haemagglutination inhibition was also demonstrated to detect antibodies. ECHO types 3, 7, 11 and 13 grown in amnion culture also caused agglutination of human cells but not of cells from sheep, chicks and guineapigs.

Associated Human Disease Syndromes

A. POLIO VIRUSES:

Bodian (1952) distinguishes 3 phases of virus multiplication: alimentary, reticulo-endothelial with associated viraemia, and neural. On this basis, five clinical syndromes produced by polio virus are recognised:

(i) *Silent infection* results when virus is present in alimentary canal only. Diagnosis in this phase cannot be made except on the basis of serological and virological evidence. Under endemic conditions, it has been calculated that latent cases outnumber paralytic ones by 100 to 1. In Chicago it was estimated that 75 per cent of children were infected once by their 4th birthday and twice by their 6th (Casey *et al.*, 1950). In Baltimore in 1947-48, there were 1000 latent cases to each clinical case (Turner *et al*, 1950). In 1954, sixty four sera from Bombay were analysed for antibodies against polio viruses (Gharpure, 1954). In sera from children under 5 years, antibodies were present against polio-1 and 2 but in sera from over 3 years antibodies were present against all the three types. A similar picture was noted in sera from Andaman and Nicobar islands (Gharpure, 1955, 1956, 1957).

(ii) *Abortive poliomyelitis* results when virus is present in the alimentary tract and there is associated viremia. This usually takes the form of a febrile illness like influenza. In children, it may cause acute tonsillitis and generalised lymph adenopathy, or it may simulate a mild upper respiratory infection with headache and non-exudative pharyngitis (Howe, 1952). The diagnosis cannot be made without demonstration of the virus and/or rising antibodies.

(iii) *Non-paralytic poliomyelitis* results when the virus from the alimentary tract after a phase of viraemia invades the nervous system but the neuronal damage is not sufficient and paralysis does not occur. The diagnosis is made on the basis of signs of viral meningitis in the C. S. fluid and serological evidence.

(iv) *Paralytic forms of poliomyelitis* vary from mild weakness in muscles to typical infantile paralysis. Bulbar forms are known to occur specially after tonsillectomy (Howe, 1952; Gharpure *et al*, 1955).

Histologically lesions are found in the anterior horn cells and to a lesser extent in the autonomic sensory columns of the spinal cord. Extensive encephalitis is present involving the motor cells of the reticular formation of medulla and pons, the vestibular nuclei and their related structures in the roof and vermis of the cerebellum. The pontine nuclei and the cerebellar hemispheres escape. In the cerebral cortex, the destruction of neurones is confined to motor and premotor areas, limited sharply by the central sulcus.

(v) *Polioencephalitis*—Snell *et al* (1957) referred to the general belief that poliomyelitis may manifest itself as encephalitis with or without paralytic symptoms. Most of the cases in the literature had been diagnosed on clinical or epidemiological grounds and only 5 cases were on record where polio virus had been isolated. Snell *et al* (*loc. cit.*) studied 121 cases of paralytic polio out of whom 9 had been labelled as encephalitis. Seven out of 9 yielded a polio virus. Frequency of polio virus isolation and the serological response as shown by neutralisation and complement fixation tests with paired sera was the same as seen in the case of paralytic polio.

B. COXSACKIE VIRUSES:

The subject of pathogenicity and the association of Coxsackie viruses with disease syndromes has been extensively reviewed in recent years by Melnick (1951); Kilbourne (1952); Melnick and Curnen (1952); Tobin (1953); Wilson and Miles (1955); Dalldorf (1955); Parrott (1957); Rhodes and Beale (1957); Sprunt (1957); Burnet and French (1958); Rhodes (1958).

(*a*) *Coxsackie A strains*—The following picture emerges regarding the probable clinical syndromes associated with Coxsackie virus A in human beings:

(i) Inapparent infection—Group A viruses have, generally, been found to be distributed in the stools of clinically healthy individuals. This is particularly true for strains which cause herpangina. In certain surveys in America the figures varied from 1·5 to 7·5 per cent of several groups of healthy or non-specifically ill patients, during the summer months. The findings have been con-

firmed by studies from Egypt, Sweden, Finland, Canada and Australia (Parrott, 1957). Parrott (*loc. cit.*) estimates an aggregate isolation rate of 4·3 per cent on the basis of the data from all these countries. In India Nanavati (1957) isolated 2 strains of Coxsackie A from stools of normal children.

Numerous studies for detecting minor illness have been carried out on healthy persons excreting Coxsackie virus A and complete absence of any clinical signs or symptoms was noted. Coxsackie A viruses have also been obtained from the faeces of infants without any indication of illness (Gear and Measroch, 1952).

(ii) Herpangina is an acute disease characterised by fever, dysphagia, pharyngitis and small ulcerative lesions on the fauces and tonsils. The disease was first described by Zahorsky (1920) and is widespread during summer months in U.S.A. particularly among children. It may be accompanied by vomiting, anorexia, abdominal pain and convulsions. Huebner *et al* (1952) showed that this disease was associated with many Coxsackie A viruses which were recovered from faeces or throat washings in 85 per cent of their cases. Isolation rate among the contacts was 40 to 60 per cent while among non-contacts it was only 3·5 per cent. A rise in homologus neutralising antibody was noted.

Numerous studies have followed and consistently the same virus strains (A-2, A-4, A-5, A-6, A-8 and A-10) have been isolated from cases of herpangina or their contacts.

(iii) 'Summer grippe'—Outbreaks of acute febrile illness lasting 2-5 days have been reported in children and adults during summer months. The disease is characterised by fever, headache, sorethroat and myalgic pains in back, neck, abdomen and limbs. A few outbreaks have yielded Coxsackie viruses in a high proportion of cases. Parrott (1957) suggested that such cases are probably, cases of subclinical herpangina.

(iv) Aseptic meningitis—Coxsackie viruses A-1, A-2, A-4, A-7 and A-10 were isolated by Johnsson (1955) from cases of aseptic meningitis. Verlinde and Tongeren (1952) isolated A-2 and A-3 from similar cases. Parrott (1957), however, doubts the validity of these data because of lack of adequate controls. Banker and Pathak (1956) isolated 21 strains of Coxsackie A virus from cases clinically diagnosed as poliomyelitis. Purandare (1955) isolated 2 strains from faeces of cases of suspected encephalitis. Brain and cord material from 16 autopsies was however, negative (Purandare, 1956).

Coxsackie A-7 and A-9 have recently been isolated from cases of aseptic meningitis (Habel *et al*, 1957). Bayer and Gear (1955) isolated Coxsackie A viruses from C. S. fluid of 3 cases of meningo-encephalitis.

(v) Diarrhoea—Association of Coxsackie A types with cases of diarrhoea and acute gastroenteritis has been reported. Parrott (1957) discounts this possibility and suggests that diarrhoea itself may be a prominent manifestation of herpangina.

(*b*) *Coxsackie B strains*—(i) Bornholm's disease—This was described by Sylvest in 1934. The disease is associated with fever, pharyngitis and muscle pain in lower thorax and upper abdomen. Atypically, mild meningitis would occur. Numerous outbreaks have been described (Dalldorf, 1955) where B viruses were isolated from throat or faeces of a considerable number of patients examined and development of antibodies demonstrated in the blood. Muscle lesions from biopsies in human cases have shown them to be similar to what is seen in suckling mice. Virus has also been recovered from them. Orchitis seems to be a fairly common complication of Bornholm's disease.

(ii) Aseptic meningitis—Rhodes and Beale (1957) point out that an intimate relationship has always existed between Bornholm's disease and aseptic meningitis. Sylvest's original paper in 1934 contains a reference to the development of 'encephalitis' as a complication in cases of Bornholm's disease. Five observations offer direct evidence for the aetiological role of Coxsackie B strains : (i) Isolation of strains of Coxsackie B viruses from stool of cases of aseptic meningitis with significant changes in the titre of homologus antibodies ; (ii) recovery of Coxsackie viruses B-2, B-3, B-4 and B-5 from C. S. fluid of cases of aseptic meningitis ; (iii) development of aseptic meningitis in laboratory workers, who were infected with Coxsackie B viruses ; (iv) rare occurrence of Coxsackie B strains in stools of normal children or of children ill with disease other than 'non-paralytic polio' or aseptic meningitis ; (v) non-recovery of Coxsackie B viruses from cases of paralytic disease.

McLeod *et al* (1956) estimated that in Toronto, 20 per cent of cases of aseptic meningitis were due to Coxsackie virus infections.

(iii) Meningo-encephalitis and encephalitis—Occasional reports of severe forms of disease with neuronal damage have been attributed to Coxsackie B infection. South African workers (Javett *et al*, 1956) found that one of their cases who died of acute myocarditis in infancy showed encephalitis histologically. Bayer and Gear (1955) isolated Coxsackie B virus from blood,

C.S. fluid and faeces of cases of meningo-encephalitis. Most of them were Coxsackie B-4. In Canada, Duncan *et al* (1955) isolated Coxsackie B-4 from C.S. fluid of 3 out of 33 patients with meningo-encephalitis. From the same series of cases, Beale *et al* (1956) isolated 13 strains of Coxsackie B-4 from faeces. Six out of 7 persons excreting the virus showed rise in specific antibodies. From Australia, Stanley *et al* (1953) described atypical strains of Coxsackie viruses which they called Coxsackie C. These strains had been isolated from cases clinically diagnosed as encephalitis and who on recovery also showed sequelae. All strains belonged to a single serological type and in contrast to Coxsackie A and B were sensitive to lysol, phenol and 20 per cent alcohol. Langdale-Smith *et al* (1957) described an epidemic of meningo-encephalitis and Bornholm's disease in which 3 groups of cases were seen ; typical Bornholm's, typical encephalitis, and a small group of intermediate types. In India Coxsackie B-4 were isolated from faeces of cases of epidemic encephalitis (Report, 1956). Paul *et al* (1959) also reported the isolation of Coxsackie B-3 and B-5 from such cases.

(iv) Other syndromes produced by Coxsackie B strains : Coxsackie B strains have been found to produce parotitis (Howlett and Sarnlo, 1957) and fatal myocarditis in infants. Coxsackie B.3 and B-4 were isolated from faeces, brain and myocardium of fatal cases (Javett *et al*, 1956 ; Kibrick and Benirschke, 1956 ; Enders, 1957 ; Delaney and Fukunaga, 1958).

C. ECHO VIRUSES :

According to recent reports (Committee, 1957) ECHO viruses are associated with following syndromes in human beings :

(i) *Aseptic meningitis* is associated with ECHO types 2 through 6, 9, 14 and 16.

Type 2 produces aseptic meningitis and was isolated from C. S. fluid in 2 cases out of four affected (Barron *et al.*, 1958). Steigman *et al* (1953) isolated virus from spinal cord of a child with fatal illness, which was later classifiable as ECHO type-2 (Steigman, 1957). ECHO-3 has been recovered sporadically from cases of aseptic meningitis (Melnick, 1957). ECHO type 4 was isolated from outbreaks of aseptic meningitis in Iowa, U.S.A., (Lehan *et al*, 1957) and in Sweden (Johnsson, 1957). ECHO-5 was isolated from spinal fluid as well as stools from patients with aseptic meningitis (Melnick, 1957).

Kirbrick *et al* (1957) found that 8/9 of their non-paralytic polio strains were ECHO-6. Davis and Melnick (1956) found ECHO-6 in 21/25 cases of aseptic meningitis ; the remaining 4 were beyond the first 14 ECHO types. Lahelle (1957) isolated 51 strains of ECHO-6 from outbreak of aseptic meningitis in Norway and in 4/7 instances it was also found in C. S. fluid. In one instance it was present in C. S. fluid but not in faeces of the same patient. Rising antibodies were also demonstrated. Von Zeipel and Svedmyr (1957) isolated 34 strains of ECHO-6 out of 130 cases of non-paralytic polio in Sweden in 1954. Neutralising antibodies against ECHO-6 were present in all patients excreting the virus. Melnick (1957) mentions that ECHO-6 had been isolated 26 times from cases of aseptic meningitis.

ECHO-9 has been reported by a large number of workers from Europe and America. It was isolated from faeces, C. S. fluid and sometimes from sputum and rising antibodies demonstrated in cases of outbreaks of aseptic meningitis with typical sings and symptoms (Mclean and Cameron, 1957 ; Baumann *et al.*, 1957 ; Godtfredsen and von Magnus, 1957 ; Hennessen, 1957 ; Klone and Korner, 1957 ; Mclean and Melnick, 1957).

In some instances, febrile illness with aseptic meningitis also showed a rubelliform or similar rash and ECHO-9 strains were isolated in numerous such outbreaks and aetiological relationship suggested (Boissard *et al*, 1957 ; Decoux, 1957 ; Laforest *et al*, 1957 ; Quersin-Thiry *et al*, 1957 ; Galpine *et al*, 1958 ; Jamieson *et al*, 1958 ; Tyrrell *et al*, 1958). ECHO-14 was isolated from cases of aseptic meningitis by Ormsbee and Bell (1957). ECHO-21 was isolated from similar cases (Rosen *et al*, 1958). In India there have been reports of isolations of ECHO viruses from cases of epidemic encephalitis (Reports, 1956 ; Paul *et al*, 1958) but their identification and role in aetiology remain to be confirmed.

(ii) *Minor febrile illness* has been found to be associated with ECHO viruses (Committee, 1957). Peterson (1957) described 2 adults with 'minor illness' from whom ECHO-9 could be isolated. ECHO type 20 was found to be associated with cases of fever, upper respiratory symptoms, vomiting and loose stools (Rosen *et al*, 1958).

(iii) *Summer rash*—According to the Committee (1957), this febrile disease with rash can be caused by ECHO types 4, 9 and 16. Neva *et al* (1954) and Neva and Enders (1954) described an exanthematous disease which occurred in Boston in 1951 from which the latter workers could isolate 7 cytopathogenic strains. In 1954, the 'Boston exanthem' disease in Pittsburg yielded similar agents (Neva and Zuffante, 1957). It was later found that these strains were related to prototype ECHO-16 (Committee, 1957).

(iv) *Summer diarrhoea of infants and children* —Ramos-Alvarez (1957) found that 24 children

out of 56 with abdominal pain, blood and mucus in stools yielded cytopathogenic agents. Of these 24 strains, 7 (29 per cent.) were found to be ECHO types, 2, 8, 11 and 12 and 3 untypables. Polio and Coxsackie viruses were also found but in controls of the same age group ; ECHOs were less common while the distribution of other viruses was the same. ECHO-7 was recovered from cases of summer diarrhoea with greater frequency (Ramos-Alvarez and Sabin, 1958). Eichenwald *et al* (1958) isolated ECHO-18 from 12 out of 21 infants with diarrhoea. This was the same as one of the untypable strains reported by Ramos-Alvarez. Serological evidence of recent infection by ECHO-18 was also produced. ECHO types 22, 23 and 24 have been isolated from cases of diarrhoea (Rosen *et al*, 1958).

Variability within the Enteroviruses

Variability due to mutation, selection in nature and recombination under experimental conditions is a well recognised phenomenon with animal viruses. Variability is also seen with enteroviruses.

(*a*) *Adapted strains of polio* involve a process of selection. Adaptation to cotton rats, mice, and chick embryos has already been mentioned. Adapted strains also show differences in their host susceptibility and behave differently in neutralisation experiments (Van Rooyen and Rhodes, 1948). Egg adapted strains of polio are known to revert back to their non-adapted state requiring primates for their growth after one passage through human or monkey tissues (Melnick, 1953) but stable chick embryo adapted strains have been produced (Roca Garcia and Jervis, 1955). Some Coxsackie A-1 strains are known to produce polio like lesions in adult mice. Coxsackie A-14 has been adapted to adult mice where it produces polio like lesions and the mouse adapted strains given intracerebrally to monkeys produces polio like lesions but no paralysis (Dalldorf, 1957b).

(*b*) *Variation in virulence*—A large number of polio virus variants with differing degree of virulence have been experimentally produced ; the inherent variability in the virus particles is aided by selective conditions like the animal host, route of inoculation and the choice of cells in culture (Syverton *et al*, 1957). Considerable effort has resulted in successful production of attenuated strains of polio virus for the production of an oral vaccine (Li *et al*, 1955 ; Sabin, 1955, 1956 ; Koprowski, 1957). However, a reversion to virulence has been observed (Dick and Dane, 1957).

Naturally occurring avirulent strains of polio virus are also known (Virlinde *et al*, 1957). Gharpure *et al* (1958) reported isolation of three non-pathogenic strains of polio, one belonging to type 1 and two of type 3. Isolation of polio viruses from healthy individuals and from diseased states may be in part dependent on variation in their virulence for their particular hosts (Gard, 1943).

Variation in growth characters with polio viruses have been noticed in connection with formalin inactivation of polio viruses. The 'inactivated' virus acquires the property of initiating very late infections in tissue cultures (Gard, 1957). Vogt *et al* (1957) reported that polio virus variants with reduced pathogenicity for central nervous system of monkeys had a low e. o. p. (efficiency of plating = ratio of the virus titre at low carbonate to the titre at high carbonate concentration in the agar used for studying plaques). Such d. (delayed) variants are being studied (Dulbecco and Vogt, 1958 ; Hsiung and Melnick, 1958b).

Lesions produced by Coxsackie B viruses vary according to the route of inoculation, adaptation and strain differences. Pancreatic lesions caused by Coxsackie B strains could no longer be produced if the virus had been passed through intracerebral transfers (Dalldorf and Gifford, 1952). Coxsackie A-9 and B viruses grow in tissue culture and on primary isolation may not be pathogenic to mice.

(*c*) *Variation in antigenic behaviour*—The presence of 'prime' strains within ECHO types 5, 6, 7, 9, 10 and 11 (Committee, 1957) which have broader antigenic reactivity than prototype strains points towards an antigenic mosaic. Similar variability has been seen with ECHO-6 in its haemagglutinating behaviour. Many strains of ECHO-6 cause agglutination of human O-group red cells but the prototype strain (D'amouri) does not (Lahelle, 1957b). Some ECHO strains produce neuronal damage in monkey while other strains of the same antigenic type do not. The variable action of ECHO-9 strains on human embryonic lung fibroblastic cultures and human amnion cultures has been observed (von Zeipal and Svedmyr, 1957 ; Quersin-Thiry *et al*, 1957).

Summary

In summary it may be stated that despite many differences, the polio, Coxsackie and ECHO viruses probably constitute one large group of enteroviruses where sharp delimitation is not possible (Committee, 1957 ; Tyrrell *et al*, 1958 ; Editorial, 1958). Apart from the habitat, these viruses have many characteristics in common. Epidemiologically they show the common seasonal

incidence, high percentage of latent infections, potential pathogenicity and universal prevalence. Physicochemically, also, they represent a closely linked group, when one considers their resistance to ether, sodium desoxycholate and to commoner disinfectants; their size, ability to stand wider range of pH and temperature variations, and inability to survive lyophilisation. Their monkey and mouse pathogenicity and behaviour in tissue culture present a picture where one group merges into another, thus emphasising their interrelationship.

The observations on various aspects of these viruses are accumulating with a speed which makes it difficult to predict as to how the present day classification of these viruses would stand the test of time (Committee, 1957).

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CASE NOTES

CHLORAMPHENICOL THERAPY IN ENTERIC FEVER ASSOCIATED WITH THROMBOCYTOPENIC PURPURA

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The value of chloramphenicol as a specific therapy for enteric fevers has been accepted all over the world. The preliminary reports based on studies in experimental animals and on human volunteers suggested that the drug had no toxic effects. In India the first mention of toxic side-effects was made by Shah (1949). Since then a large number of minor and major toxic effects have been reported. Amongst the major toxic effects, agranulocytosis, thrombocytopenia and aplastic anaemia resulting from the depression of the bone marrow by the drug have been reported. As far as the author is aware there are no reports on the use of chloramphenicol in cases of enteric fever associated with thrombocytopenic purpura, agranulocytosis and aplastic anaemia. The present paper is a report of one case of typhoid fever associated with thrombocytopenic purpura treated successfully with chloramphenicol.

CASE REPORT

A girl, aged 11 years, was admitted to Sir H. N. Hospital, Bombay, on 22-7-1959 for continuous fever for 3 days. The illness started one month ago when she had remittent fever lasting for two weeks. She did not receive chloramphenicol or any other antibiotic during the period. She remained afebrile and well for a fortnight and had a relapse of fever form which she was suffering for the last 3 days. Her mother stated, the girl was deaf and dumb since infancy.

There was nothing contributory in her past illness or family history.

On examination her temperature was 102°F., the pulse rate was 110 per minute and respiration 28 per minute. The tongue was coated and there were no other physical findings. A clinical diagnosis of enteric fever was made. On the next day bleeding from the gums was noted which increased on the third day. On the fourth day, besides bleeding from the gums, there was petechial haemorrhage in the skin and she passed reddish urine.

Laboratory investigations—During this period the red cell count was 4·12 million per c.mm., haemoglobin 70 per cent, W.B.C. 4,900 per c.mm. with neutrophils 38 per cent lymphocytes 58 per cent, eosinophils 2 per cent and monocytes 2 per cent.

The urine showed presence of albumin and red blood cells, 20-25 per field.

The Widal test was positive for *S. typhosus H* in dilution of 1 in 125.

On the fourth day of admission her platelet count was 8,900 per c.mm. and the bleeding time was 10 min. 32 sec. The clotting time was 5 min. 4 sec. and prothrombin time 13 sec.

Diagnosis of typhoid fever associated with thrombocytopenic purpura was made.

The patient was treated with prednisolone 30 mg. per day from 25-7-1959, combined with penicillin, folic acid and vitamin B_{12}. Two blood transfusions of 300 c.c. each were given. During this period the fever appeared to be settling down but showed irregular and slight rises. But the bleeding from the gums, skin and urinary tract continued and the patient developed typhoid state. The results of repeated platelet counts, and study of bleeding time and clotting time during the week are shown in Table 1.

TABLE 1—SHOWING RESULTS OF SERIAL BLOOD EXAMINATIONS (BEFORE CHLORAMPHENICOL)

Date	Platelet count per c.mm.	Bleeding time		Clotting time		Widal test
		Min.	Sec.	Min.	Sec.	
25-7-59 ...	8,640	10	32	5	4	Positive (1 in 125)
27-7-59 ...	4,560	7	10	6	20	Positive (1 in 500)
29-7-59 ...	8,240	15	55	5	10	...
1-8-59 ...	4,200	15	20	4	10	Positive (1 in 500)

The urine showed persistent and marked haematuria. The prothrombin time was 13 sec. The other liver function tests were within normal limits, e.g., Takata-Ara was negative, thymol turbidity was 4 units and serum alkaline phosphatase was 2·5 Bodansky units. The bone marrow obtained by sternal puncture was found to be unsuitable for proper interpretation. The Widal test which was initially positive 1 in 125 was noted to be positive 1 in 500 on 27-7-59, and 1 in 500 again on 1-8-59.

Chloramphenicol was withheld upto 1-8-1959 when it was decided to administer it in spite of marked thrombocytopenia. On the first day a test dose of 250 mg. three times a day was given. From the subsequent day a dosage of 2 g. of chloramphenicol divided in four equal doses (roughly estimated at 50-60 mg./Kg.) was administered for the first two days and in diminishing dosage later on, making a total of 9·5 g. in 12 days. Prednisolone was continued in a dosage of 15 mg. per day for 3 days, and then in lower dosage. During the first two days the patient started showing improvement as judged by temperature remaining normal, diminution of bleeding from mouth, improvement from typhoid state and diminution in microscopic haematuria with its disappearance on the third day of chloramphenicol therapy. The platelet count, bleeding time and clotting time during the chloramphenicol therapy are noted in Table 2.

TABLE 2—SHOWING RESULTS OF SERIAL BLOOD EXAMINATIONS (AFTER CHLORAMPHENICOL)

Date	Platelet count per c.mm.	Bleeding time		Clotting time	
		Min.	Sec.	Min.	Sec.
3-8-59 ...	23,240	...		...	
5-8-59 ...	16,160	3	10	4	00
8-8-59 ...	49,920	3	55	6	45
11-8-59 ...	100,280	3	10	5	20
17-8-59 ...	184,000	3	20	5	00
28-8-59 ...	198,240	2	30	4	05
3-9-59 ...	193,920	2	10	3	10

Subsequently, the patient made an uneventful recovery and left the hospital on 7-9-1959, making a total hospital stay of 48 days and convalescent period of 35 days. The clinical progress of the case is graphically represented in Fig. 1.

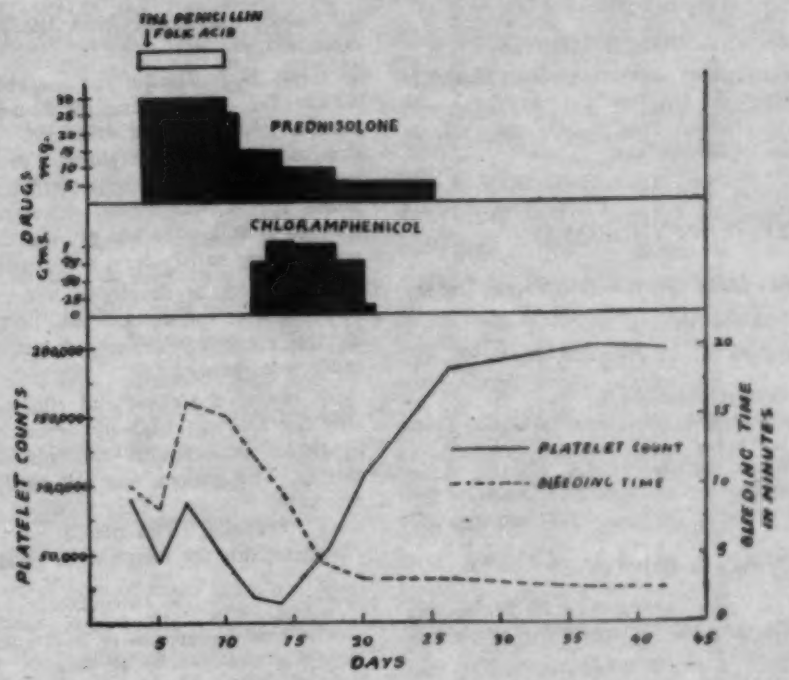

FIG. 1—GRAPHICAL REPRESENTATION OF THE CLINICAL PROGRESS OF THE REPORTED CASE

COMMENTS

The diagnosis of typhoid fever in this case, even in the absence of isolation of typhoid bacilli in culture is the most probable one, based on the clinical findings and the Widal's test showing a rising titre of 1 in 125 on 24-7-59 to 1 in 500 on 27-7-59 and again 1 in 500 on 1-8-59. The associated thrombocytopenic purpura did not result from chloramphenicol or any other toxic drugs, since the drug therapy, prior to appearance of bleeding gums, consisted on a diaphoretic mixture. Thrombocytopenic purpura in this patient was probably due to bone marrow depression by typhoid infection. The inhibition of bone marrow in typhoid fevers has been well documented (Wintrobe, 1956). It is explained on the basis that the cellular reaction of large mononuclear phagocytes excited by typhoid bacilli may invade the red bone marrow and may interfere with normal haemopoiesis. These abnormal cellular infiltrations may obliterate the megakaryocytes or may so alter the bone marrow metabolism as to render the megakaryocytes non-proliferative. This possibility appears to be well supported by the fact that there was a prompt and definite response to chloramphenicol therapy instituted after an unsuccessful regime of combination of prednisolone, penicillin, folic acid, pyridoxine and two blood transfusions, lasting for a week (Fig. 1). During this week, the patient showed increasing toxaemia, the purpuric haemorrhages continued unabated, the repeated platelet count remained low (from 8,040 on 25-7-59 to 4,200 on 1-8-59) and the bleeding time remained raised to abnormal levels.

The decision to use chloramphenicol in a case with marked and persistent thrombocytopenia was both difficult and full of possible harmful effects. But it was clear that though the aetiology of associated thrombocytopenia could not be determined, it was certainly not due to chloramphenicol, since the history was definite that she was not given the drug any time previously. The probable harmful depression of the bone marrow by the drug was weighed against the risk of not giving the only known specific drug for typhoid infection. It appeared from the results that the decision was correct. In taking the difficult decision the author had the experience of his previous report on the observations of the effect of chloramphenicol on the depressed bone marrow in enteric cases in which it was noted that the drug did not worsen the depressed bone marrow but seemed to be beneficial (Shah *et al*, 1956).

The conclusion is obvious that there should be no hesitation in the use of chloramphenicol in typhoid fever associated with marked thrombocytopenia, provided due care is taken to elicit a thorough inquiry that the thrombocytopenic state has not followed the previous use of chloramphenicol.

SUMMARY

A case of typhoid fever associated with thrombocytopenic purpura treated successfully with chloramphenicol is reported.

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TEITZE'S SYNDROME

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This condition first described by Teitz in 1921 is characterised by benign, painful, non-suppurative swellings, affecting the upper costal cartilages.

It is not associated with any trauma, infection either specific or non-specific or any neoplastic condition.

Two cases encountered in this hospital are reported.

CASE REPORTS

CASE 1—A Hindu female, aged 19 years, was admitted in this hospital for treatment of pulmonary tuberculosis.

On admission her general condition was good. The sputum was negative for A.F.B. The skiagram of the chest showed productive type of lesion affecting the right upper zone. The left lung was free.

She was put on chemotherapy and was progressing well. On 4-2-59 she complained of acute pain in her left chest.

On examination the pulse rate was 120 per minute and the respiration 25 per minute. The temperature was 98·6°F.

Breath sounds could be heard over both the lungs and no adventitious sounds were detected. There was some tenderness on the left 2nd costochondral junction. A small swelling appeared at this spot later on.

Treatment—She was put to bed rest and analgesic tablets in the form of codopyrine and sodium salicylate mixture 1 oz. t.i.d. were administered. Liniment A.B.C. was applied locally.

She came round gradually, the pain and tenderness over the said area having diminished. The swelling also subsided remarkably. The succeeding examination—skiagram of chest did not show any particular change except some residual lesion of fibrotic type in the right upper zone. The B.S.R. was within normal limits. Though the pain and tenderness diminished, the swelling persisted for more than 4 weeks. The patient was ultimately discharged from the hospital in good condition.

CASE 2—A Hindu, male, aged 23 years, was admitted in the hospital on 22-6-57 for the treatment of pulmonary tuberculosis. At investigation skiagram of the chest showed productive type of lesions involving the upper zone of the left lung field. E.S.R. was 8 mm. The sputum was negative for A.F.B. He was put on chemotherapy and was making satisfactory progress.

On 8-3-58 he developed a firm painful round swelling over the anterior end of the left third rib at the costochondral junction. There was no other symptom.

X-ray of the chest and ribs revealed that the swelling was not of bony or cartilaginous origin. Systemic examination did not contribute anything. The patient was put on local and symtomatic treatment. The swelling subsided after about 8 weeks. The patient was ultimately discharged from the hospital in good condition.

DISCUSSION

This condition appears to be of more clinical interest than of any pathological significance. It is likely to remain unnoticed and the importance of the condition in these cases particularly in the first one lies in the fact that it may simulate pleurisy, intercostal neuralgia and localised tuberculous infection of the rib. The second case might be confused with any growth either bony or cartilaginous.

The first case had a sudden onset with pain followed by swelling of the 2nd left costochondral junction. The pain was relieved by analgesic tablets and local application of anodyne. The pain was relieved within 3 days but the swelling persisted for more than 4 weeks.

The second case was not so acute in onset, possibility, of any growth in that region was ruled out after the x-ray examination. The swelling also subsided on local and symptomatic treatment. Here the swelling persisted for more than 8 weeks.

The view, that deficiency of vitamin B complex and vitamin C has some bearing in the causation of the condition (Evans and Eames, 1952), is not reconcilable in these cases as the patients were already getting vitamin B complex and vitamin C as a routine. Some authors suggest that an infiltration with hydrocortisone or related steroids into the involved area may relieve the discomfort to some extent.

ACKNOWLEDGMENT

I am grateful to Dr. U. C. Sarkar, Superintendent of Kanchrapara T. B. Hospital, for kindly permitting me to report these two cases and Dr. B. Mukherjee for valuable suggestions.

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LEUKAEMIAS

During recent years the incidence of leukaemia appears to have increased in Western countries and in Japan[1-9]. A rising trend is seen in India also[10]. Increasing awareness of the condition and better diagnostic facilities are no doubt bringing to light many of the cases which would previously go unrecognised. An absolute increase in the incidence of the disease is also possible. Although the available data do not provide any unequivocal proof of an absolute increase in the incidence of leukaemias, certainly more of these cases are seen at present than at any time before. With the control of communicable diseases, the disease pattern is changing in the country. In this changing pattern, in years to come, leukaemias and allied disorders would hold a relatively important position.

Ionising radiations, atomic explosions, newer drugs and all sorts of 'new things' in the environment have been incriminated as leukaemogenic agents. That ionising radiation can cause leukaemia in man and in experimental animals is now well established. The unequivocal evidence in favour of leukaemogenic effect of radiation has been provided by a significant increase in the incidence of leukaemia in the following five groups of subjects who had received heavy exposures: (a) survivors of the atomic explosion at Hiroshima and Nagasaki in Japan, (b) patients who received radiotherapy for ankylosing spondylitis, (c) infants who received radiotherapy for their thymic enlargements, (d) babies born of mothers who received radiotherapy during pregnancy and (e) radiologists[6, 9]. In recent years there have appeared a large number of reports and reviews on the specific role of radiation in the causation of human leukaemia. While not questioning the leukaemogenic effect of radiation, it may be pertinent to recall that leukaemia is an ancient disease. It had been in existence long before the introduction of x-rays either for diagnostic or for therapeutic purpose. In an average case of leukaemia seen in clinical practice, it is difficult to incriminate x-rays as cause of leukaemia. It seems unlikely that variations in exposure either to natural or man-made radiations could account for more than a fraction of the increase in the incidence of leukaemia as reported over the last two or three decades[9]. It should also be mentioned that most of the reported increase in the incidence of the disease is due to increase of the lymphatic and not the myeloid variety which is known to be induced by x-rays. In Western countries, leukaemia has been reported to be more frequent in the rich than in the poor[1, 4]. Data in the Indian series do not suggest that leukaemia is particularly common in the wealthier sections of the Indian community[10]. The large number of patients seen in the poorer section of the Indian community would indicate that the disease cannot have any predilection for the rich. Dietary habits, place of residence, infections, exposure to myelotoxic drugs, x-rays and ionising radiation do not appear to play any aetiologic role in the causation of leukaemias as seen in Indians[11]. Thus the observed association between high leukaemia rates and high standards of living and medical care may possibly have no more causal

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significance than that incidental to variation in diagnostic procedures. In this connection mention must be made of a speculative hypothesis recently advanced by Stewart and Hewitt[9]. During recent years, a large number of subjects, particularly infants and elderly people, are regularly saved from infections which in pre-antibiotic era would certainly have been fatal. This new class of 'survivors', whose number is increasing, may have an increased liability to leukaemia[9].

The various types of the disease described under the common term leukaemia differ significantly from one another. In this aetiologically obscure group of disorder, it is worthwhile to take note of all the variations from one type to the other. In spite of many apparent similarities, the various types may not be closely related aetiologically. While there is some general agreement regarding the increase in the incidence of the leukaemias, there is considerable controversy regarding the relative increase in the frequency of the different types. It is the general impression that chronic lymphatic leukaemia has been increasing more rapidly[2], and the increase is more in favour of the acute than the chronic type.[6] In this context, it may be mentioned that chronic lymphatic leukaemia is relatively rare in Africans and Asians. In a series of 307 cases of leukaemia in Indians, there were only 17 cases of chronic lymphatic leukaemia[11].

In spite of the large volume of literature that has accumulated on human leukaemia, the disease still remains an enigma from the aetiological standpoint. Virus theory has failed to establish itself. The possibility of somatic mutation as a cause of cancer[12] has recently[13, 14, 15] received a great impetus. The theory of 'clonal selection' and 'auto-immunisation' may be advanced to explain the abnormal cellular proliferative process that characterises this disease. The various leukaemogenic agents may conceivably induce the development of a new 'race' of cells, possibly by enzyme deletion, leading to somatic mutation. It is possible that in the genesis of leukaemia, the intrinsic host factor is no less important than the various leukaemogenic agents. This concept of mutation of somatic cells, if true, would bring in a pessimistic outlook in so far as the control and cure of leukaemia are concerned. If the disease had a viral background, the prospect of a chemotherapeutic conquest could be expected with a reasonable amount of optimism. Against a lesion at the genetic level, chemotherapy alone may fall short of expectation. Bone marrow infusion following massive irradiation is also unlikely to solve the problem of human leukaemia. It appears that the concept of auto-immunisation has a more than theoretical interest in any comprehensive programme against the control of this still uncontrollable disease. The course of a self-replicating proliferative process perpetuated on an auto-immune basis may be modified by the stimulation and augmentation of the 'anti-proliferative' host factors which would normally guard against any abnormal or aberrant cellular proliferation. Some work in this direction has already been done[16] in the treatment of neoplastic diseases involving mainly the female genital organs. Here an auto-vaccine prepared from tumour cells with Freund's adjuvant was used. The initial result though not spectacular is full of promise. A similar approach in the treatment of leukaemia is worth striving for. This therapy may not, however, work alone. In conjunction with suitable chemotherapy, a properly prepared 'cellular vaccine' may prove useful in prolonging and fortifying a remission.

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CURRENT MEDICAL LITERATURE

Eosinophilic Pleural Effusion

JARVIMEN AND KAHANPAA (*Acta med scandinav.*, **164**: 245, 1959, Ref. *J. A. M. A.*, **172**: 82, 1960) investigated long-term results in 17 patients with eosinophilic pleurisy, either idiopathic or associated with a transitory pulmonary infiltration. The degree of pleural eosinophilia varied from 11 to 70 per cent. The pleural exudate of 10 patients contained blood. Simultaneous eosinophilia of the blood was found in 10 patitnts. The cure in patients with eosinophilic pleurisy was generally more rapid, even in the absence of specific therapy, than that usnally obtained in patients with idiopathic exudative pleurisy. The average duration of hospitalisation was 43 days.

To determine the long-term results in patients with eosinophilic pleurisy, follow-up examinations were made 5 to 12 years after the onset of the disease. Two patients had developed pulmonary tuberculosis. This morbidity must be considered low compared with that of patients with idiopathic exudative pleurisy. A control study showed that pulmonary tuberculosis developed in 21 of 52 such patients, or 40 per cent. Pleurisy recurred in two of the patients with eosinophilic pleurisy. The results of the investigation suggested that eosinophilic pleurisy was fairly strongly sex-linked, as 15 of the 17 patients were male. There was an antecedent respiratory infection in 10. Four patients had a co-incidental peptic ulcer. Bronchial asthma appeared later in two patients. The prognosis appeared to be good and primary recovery was more rapid than in patients with ordinary exudative pleurisy. The fact that the pleural exudate contained blood in 10 of the 17 patients studied often causes the clinician erroneously to suspect malignant neoplasms or pulmonary infarction.

Anal Lesions in Crohn's Disease

MARSON, B. C. AND LOCKHART-MUMMERY, H. E. (*Lancet*, **2**: 1122, 1959) from St. Mark's Hospital, London, write that 23 cases of Crohn's disease had anal fistulae or fissures, and in 10 the clinical appearance of the anal lesions suggested tuberculosis.

Tissue from the anal lesions was examined histologically in 12 cases and found to contain non-caseating giant-cell systems similar to those in the intestinal lesions of Crohn's disease.

Thus when a pathologist finds giant-cell systems in histological material from an anal fistula, Crohn's disease should be considered in the differential diagnosis.

Retinal Haemorrhage in Severe Anaemia

COSNETT, J. E. AND MACLEOD, I. N. (*Brit. M. J.*, **2**: 1002, 1959) from Durban write that during an analysis of 74 cases of severe anaemia among Indians the retinal appearances were studied in relation to the type and severity of the anaemia. It was found that retinal haemorrhages occur almost universally in severe megaloblastic anaemia and in anaemia associated with thrombocytopenia. Retinal changes occur rarely in cases of iron-deficiency anaemia or anaemia due to blood loss.

Though this sign has been mentioned previously, it is felt that its value has not been sufficiently emphasised. It is diagnostically useful in communities where severe anaemias of these types are prevalent.

Continuous Antibiotic Treatment of Chronic Bronchitis

MUDROCH, J. MCC., LECKIE, W. J. H., DOWNIE, J., SWAIN, R. H. A. AND GOULD, J. (*Brit. M. J.*, **2**: 1277, 1959) of Royal Infirmary, Edinburgh and Department of Bacteriology, University of Edinburgh, gives below the summary of their observations on the results of continuous antibiotics in chronic bronchitis:

Two double-blind trials of continuous daily tetracycline-oleandomycin and oxytetracycline treatment in patients with chronic bronchitis were carried out during the winters 1957-8 and 1958-9 respectively. Twenty-three patients were observed in the first trial and 75, including 20 from the former, were seen in the second.

The antibiotic-treated groups were greatly benefited as compared with the groups receiving 'dummy' capsules. Improvement was judged on the basis of reduction in the number and severity of acute exacerbations, by eradication of *H. influenzae* and pneumococcus from the sputum, and by statistical comparison of sickness in the treated as against the untreated groups.

Serial sputum examinations were of value in the assessment of each patient's progress, but single specimens did not necessarily reflect the condition, since H. influenzae and the pneumococcus were not isolated from every specimen.

A significant rise in antibody titre to the influenza viruses was demonstrated in 14 patients during the second trial, but only 3 of them had clinical influenza. Subclinical infection in the remaining 11 did not obviously affect their bronchitis.

Side-effects were infrequent and not serious. Diarrhoea was mildly troublesome in 15 out of 47 patients receiving antibiotics.

Gross disturbance of normal surface flora of the respiratory and intestinal tracts was not evident. Antibiotic-resistant strains of coliform species and *Staph. aureus* occurred in some patients, mainly in those receiving antibiotics, but they were not significantly associated with clinical deterioration.

It was found practicable to manage the patients on an out-patient or domiciliary basis. This had the advantages of a lower overall cost than hospital treatment, which, in any case, carries with it the attendant dangers of superinfection with antibiotic-resistant and often highly virulent micro-organisms. It is therefore preferable, should exacerbations of bronchitis arise, to treat them in the home rather than to seek immediate admission to hospital. It is concluded that continuous daily oxytetracycline therapy in advanced cases of chronic bronchitis, though apparently expensive, is less costly than the treatment of exacerbation of the disease in hospital. It is also safe and can be recommended as a reliable method of preventing such exacerbations.

Intravenous Tetracycline of Pyelonephritis with Hypertension

BOHN, H. AND KOCH, E. (*German M. Monthly*, **5** : 8, 1960) from the Medical and Neurological Clinic, University of Giessen in reporting on the results of 6 years of treating pyelonephritis with or without hypertension by means of intravenous administration of tetracycline observe :

Every acute initial attack of pyelonephritis can be completely cured; an acute exacerbation in the course of chronic pyelonephritis can be similarly cured; even a fulminating course with *E. coli* septicaemia can be converted into a mild latent form of pyelonephritis.

The treatment with pyrrolidinomethyl-tetracycline should be started as early as possible; no other drug or combination of drugs has, in the authors' experience, given comparable results. In some patients with pyelonephritis and apparently fixed hypertension, not only the general disease but also the hypertension have been favourably influenced. There occurred a rapid fall of blood pressure to normal or almost normal levels. Usually this antihypertensive effect of pyrrolidinomethyl-tetracycline was noted only while the drug was given. If the blood pressure rose again after conclusion of one course of tetracycline administration, renewed treatment again led to the reduction in blood pressure. In some instances the reduction of the blood pressure, thought to be "fixed" at hypertensive levels, lasted for up to 2 years.

The usual dosage consisted of one or, at most, two injections of 250 mg. daily for 8-12 days (total dose of 2-3 g.) no untoward reactions were noted.

Hydrochlorothiazide in Cirrhosis of the Liver

RISSEL, E. SCHNACK, H., STEFENELLI, N. AND WEWALKA, F. (*German M. Monthly*, **4** : 423, 1959) from the First Medical Division, University of Vienna, Austria, observe :

Hydrochlorothiazide was given to 20 patients with cirrhosis of the liver and ascites. In 18 patients, receiving 150 mg. of the drug daily for 3 days, there occurred an average weight loss of 3·1 kg. with the urinary excreteion of chloride and sodium, while there was little loss of potassium. There was little, if any, inhibition of carbonic anhydrase. The diuretic effect persisted for another day or two after administration of the drug had ceased, and it continued even after the prolonged intake of 50 to 150 mg. daily. The drug was well tolerated even during prolonged administration, and there was no rise in blood ammonia concentration even in patients with severe cirrhosis.

Drugs in Emotional Disorders

HOLLISTER, L. E. (*Ann. Int. Med.*, **51** : 1032, 1959) from the Medical Service, Veterans Administration Hospital, Palo Alto, California in dealing with drugs in emotional disorders, past and present, observes :

The present crop of drugs for treating emotional illnesses follows a long list of previous pharmacologic treatments. The chief difference is that some of the newer agents are far more useful than any past drugs. The three broad categories of psychopharmacologic agents are : (1) tranquillisers, (2) antidepressants, and (3) psychotomimetics. As with previous drugs, the aims of therapy are similar : calming disturbed behaviour, relieving symptoms of mental depression, and facilitating psychotherapy.

Tranquillising drugs fall mainly into four groups, though rapidly increasing in numbers. Phenothiazine derivatives and Rauwolfia alkaloids are new types of compounds, both in chemical structure and in pharmacologic actions. Diphenylmethane and glycerol derivatives are related to previous drugs and differ in many respects from the other two groups. While tranquillising drugs have proved to be effective for a wide variety of emotional illnesses, most importantly the schizophrenic reactions, their utility is limited.

A revival of interest in the hydrazide derivatives has started a search for other agents with antidepressant properties. A new series of iminodepressant agents are still not fully assessed, in part because of the generally favourable course of mental depressions.

The psychotomimetic drugs have been used chiefly as tools for exploration of the mind (often with some notoriety), as well as for facilitating psychotherapy. The relevance of the abnormal mental states produced by them to schizophrenia has been challenged by many investigators. Just how useful these drugs will be as experimental tools remains to be determined.

Mediastinal Masses

LYONS, H. A., CALVY, G. L. AND SAMMONS, B. P. (*Ann. Int. Med.*, **51** : 897, 1959) from the Department of Medicine, State University of New York, College of Medicine, Downstate Medical Centre, and the Departments of Medine and Radiology and Medicine, U. S. Naval Hospital, St. Albans, N.Y., and the Second Pulmonary Disease Division, Kings County Hospital, Medical Centre, Brooklyn, N.Y. from a study on 782 cases observe :

Mediastinal masses may be neoplastic or non-neoplastic. The neoplasms may be benign or malignant, and are dangerous, especially when undiagnosed. Because of the close contact of vital structures in the mediastinum, threatening complications can occur, and the possibility of malignancy is always present with a mediastinal tumour. Of the entire group of 782 cases, 42 per cent were histologically malignant, and many others were life endangering because of size or position. The mediastinal tumours must be differentiated—and usually can be—with the use of modern diagnostic aids. The scalene node biopsy and angiocardiography are two essential diagnostic procedures, and their use may prevent needless exploratory thoracotomy. Angiocardiography gives information about the feasibility of operation, or, in fact, evidence to contraindicate an operation.

Thoracotomy is mandatory, and should not be delayed when other methods cannot establish the diagnosis. Thoracotomy has a low case fatality rate, offers cure in benign lesions, and gives accurate information on the histologic nature and the gross involvement by the tumour. This permits intelligent management and provides valuable information for prognosis.

CURRENT TOPIC

The following is from the Presidential Address by Dr. R. V. Sathe at the Fifteenth Conference of the Association of Physicians of India held at New Delhi in January 1960.

The Medical Council of India has played a significant role in the orderly growth and development of the medical institutions of our country. The Council has laid down standards for the buildings and equipment of the various departments of the medical colleges, the minimum requirements in the personnel and staff of these departments, the standards of qualification and experience of teachers and the requirements of the number of beds and facilities for training and research available in the hospitals affiliated to these colleges. By the Indian Medical Council Act, 1956, which has come into force recently, the Council has been entrusted with responsibility for maintenance of standards in post-graduate medical education. The Government of India has appointed a Postgraduate Medical Education Committee with Dr. B. C. Roy as its Chairman for the assessment of facilities existing for Post-graduate Education and to make its recommendations. This will considerably help the Post-graduate Education Committee of the Council to plan its work.

Our Association has been keenly interested in these developments since 1945 and has taken great interest in the formation and development of these institutions and in the various problems connected with the same. The requirements of pre-medical training, the methods of selection for entrance to the medical colleges, the simplification of the curricula of the pre-medical subjects, the problem of didactic lectures *versus* the practical training in the laboratory and at the bed-side, the methods of examination and the desirability of giving credit for the day-to-day work of the students have all engaged the attention of our members during these years.

With the rapid increase in the number of institutions, new problems have arisen which need attention.

Post-Graduate Medical Education

Many of the new colleges have been so much absorbed with the teaching of the undergraduate students, that they have not been able to attend to the development of post-graduate training in their institutions. The graduates from these institutions, who wish to take postgraduate training do not find facilities for these in their own institutions. They have therefore to migrate to distant places, with fully developed centres for post-graduate studies. At these centres they are not eligible to get resident posts and they have to depend on their own finances for this training. This entails considerable hardship on these students. The recent trend of increasing this period of post-graduateship from two to three years before post-graduates could take their degrees and the rise in the cost of living further add to their difficulties. As a result, many of these students are prevented from taking up post-graduate training or from pursuing it successfully. In course of time, all institutions should be able to provide facilities to their own post-graduates. But till that time, these post-graduates from our sister institutions deserve sympathetic consideration. The host institutions should take particular interest in them; and the deserving ones among them should be provided with suitable resident posts or facilities which will enable them to take higher post-graduate training and qualifications.

The striking advances in the basic sciences—physics and chemistry—have led to parallel activity in the application of these to the various fields of medicine. This has led to phenomenal advances in the knowledge of life processes in health and disease and in the management of the latter. It has led to considerable expansion of the fields of study to be covered in the respective branches by the post-graduate students. It has been more and more difficult to cover these fields in the short period of two years. And many Universities in this country have found it necessary to extend this period from two to three years. The Indian Medical Council has already advised to the same effect in 1952. But it appears, even this extended period may not suffice. And in many foreign countries this period extends to four or five years. This extension of post-graduateship from two to three years has already shown repercussions in some institutions, where the number of post-graduate students is getting smaller. And this has been mostly due to economic considerations. Residentships, part-time appointments, fellowships and stipends with facilities to do post-graduateships ought to be provided. It is therefore surprising that in some of the institutions where such facilities existed previously, they have been curtailed. Unless such facilities are afforded, post-graduate students may find it well-nigh impossible to undertake their studies.

Research and Training of Teachers

The coming up of a large number of medical colleges in the last few years has posed another problem, that of the paucity of teachers, satisfying the requirements of the Indian Medical Council. Difficulties are thus experienced in having our young colleges adequately staffed with teachers. If the teachers have the necessary academic qualifications, they lack teaching experience for the stipulated number of years. Many of our young doctors who have obtained post-graduate qualifications here or abroad are thus disqualified from holding these posts. Some of the old teachers do not possess the necessary qualification, though they have been excellent teachers. It is desirable that the Council should relax the standards of qualifications or of the period of experience, in individual cases, during the transition period. In spite of these measures however, we shall need more and more teachers for the future and we must have proper plans laid for the development of teachers in our country.

Every teacher today and in future should be an investigator also and should have some experience of research. Research does not necessarily mean great discoveries. But it means a systematic effort to understand things not so far understood and to find out things not so far known. It is a discipline which trains a person for proper planning, working out details, taking

help of the colleagues in fields of work where it is needed, systematic observation, proper recording, proper thinking and arriving at conclusions. Such a type of work is a stimulating experience to the research worker. When such a person teaches it clears his own thoughts and ideas and makes him a better teacher. Every research worker ought to teach and every teacher ought to be a research worker.

The type of research mentioned above requires in addition to the qualities and efforts of the person concerned, well-equipped laboratories and some personnel. Besides an atmosphere of research is also conducive to it. The various teaching medical institutions may provide these to a varying extent. But there should be centres in the country affording these facilities in ample measure, which should serve as centres for the training of teachers. The All India Institute of Medical Sciences at New Delhi is one such institution which aims at providing facilities and the atmosphere for research and which has as its aim the training of post-graduates and development of teachers. I believe, the recently started post-graduate college at Calcutta is also designed to run on similar lines and for similar objects. But we need some more institutions of this type, preferably situated in different parts of our country, in the larger centres of medical teaching.

Besides these institutions for the training and development of teachers, other opportunities that are available today must be utilised. A number of institutions in our country are doing specialised work of a high order. The Haffkine Institute, Bombay, the King Institute, Guindy, Madras, the Nutrition Research Laboratories at Coonoor, the Central Research Institute at Kasauli, The School of Tropical Medicine and the All India Institute of Hygiene and Public Health at Calcutta, may be mentioned as examples. There are reputed centres working on the problems of cancer, leprosy and tuberculosis. Work of high order is being done in the fields of neurology, neurosurgery, cardiology and chest surgery. At least at one place good work on allergy has been going on. Our post-graduates and teachers may be given opportunities to spend a few weeks to a few months at these places. Wherever possible these visits could be arranged in the vacation periods. Such visits would acquaint these post-graduates with the details of the work done in the various centres in our country. It would broaden their outlook and stimulate and enable them to initiate and develop similar centres in their own places. There are teachers of repute and workers with work in special fields to their credit, in the different parts of our country. Exchange programmes could be suitably arranged so as to afford the benefit of such teachers and workers to the students—undergraduate and postgraduate—at different places. It would also afford opportunities to these specialist workers to study interesting problems by observations on the spot. These programmes of exchange of teachers and specialised workers and the programmes of short and long visits to different institutions doing special work, can be carried out conveniently in the case of full time teachers.

In all institutions today there are full time teachers in pre-clinical subjects. Some difficulty however, is experienced in the recruitment of teachers for these subjects due to the scales of pay offered. These scales should be revised and made attractive so that the teachers could live with freedom from want. Then only shall we be able to get the best of teaching in these fundamental subjects. The teachers in clinical subjects have very heavy responsibilities of teaching the expanded medical curricula; besides they need time to devote to research work. It is therefore very desirable that teachers in clinical subjects also should be full time workers. And this is already so in many of the new colleges. But these teachers in clinical subjects are also unhappy with the remunerations offered and often change their positions for better alternatives. They ought to be adequately paid. And this is so difficult in our country today, which is economically poor. A limited number of consultations within the premises with some remuneration is a proposal worth serious consideration, under the circumstances.

Honoraries

At some well-developed centres of medical education, we have a large number of consultants, who have been giving their services to the medical colleges and hospitals in an honorary capacity. Many of them are highly qualified and have earned reputation in their profession. Their contribution to the hospitals and teaching institutions has been considerable and commendable. They should continue to serve in such institutions. They could also profitably work in coordination with the existing full time teachers as is being done in several educational centres in the West. This will reduce the financial load on these institutions.

Hospitals

The hospitals affiliated to the medical colleges should have some provision of beds for paying patients. There are many patients who would like to be treated by the specialists and experienced clinicians working in these institutions. However, they may not like to be treated as free patients. By providing such paying beds, these patients get the opportunity of being looked after by men of eminence. And the hospitals would benefit appreciably by the payments so received. This income could be spent towards the provision of better amenities at these hospitals and towards the provision of equipment and facilities for research in these institutions. In most of the institutions in Western countries such a pattern exists in the teaching hospitals and works to the benefit of the institutions concerned as well as the patients in these institutions.

It would not be out of place here to refer to the possibility of provision of District Hospitals in the near future. These hospitals will have a strength of 100 beds each and will be manned with specialists in every branch, to provide medical care to the rural population of the districts. There would be about 250 such district hospitals and according to estimates, the number of specialists required would run into several thousands. The suggestions made above towards the development of teachers would also serve towards the development of these specialists.

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NOTES AND NEWS

Hopeful Results of Mass Campaign with Live Polio Vaccine

Mass vaccination campaigns using live poliomyelitis vaccine given by mouth have demonstrated the safety and probable effectiveness of this new method, according to an article in the latest *WHO Chronicle* (Vol. 14, No. 4, April 1960) published by the World Health Organisation.

For some years research workers have been trying to produce a poliovirus vaccine that would give maximum protection without untoward side effects. Several attenuated live vaccines have been developed to this end, by Sabin, Koprowski and Cox, and by 1957, work was sufficiently advanced to permit the WHO Expert Committee on Poliomyelitis to recommend that large scale trials be undertaken. In the ensuing two years, limited trials of the live vaccine were carried out in family groups and children's homes in the U.S.A., Poland, Sweden and the U.S.S.R. The larger groups were vaccinated, 3,000 children in Mexico, about 150,000 in Czechoslovakia, and 200,000 in Singapore.

After a number of trials in both Moscow and Leningrad which produced strong evidence of the vaccine's harmlessness and efficacy, the U.S.S.R. Ministry of Health authorised general use of the vaccine, and, by the end of May 1959, it had been administered to several million children in various republics of the U.S.S.R.

Studies in these countries revealed information of great value in the assessment of live poliovirus vaccine. In the U.S.S.R., for example, not only was there good evidence that the vaccine caused no ill effects, but in certain republics, the incidence of poliomyelitis following its use was much lower than in the previous five years.

In Leopoldville, on the other hand, where the most susceptible population group, African children under 5, was vaccinated in 1957, as well as in some trials in Latin America, "wild" enteroviruses, often present in the intestines of the vaccinated persons in such areas, probably interfered with successful immunisation by the poliomyelitis vaccine virus.

The phenomenon of interference between viruses helps to create a paradoxical situation in poliomyelitis protection. In environments where hygiene is at its highest and overcrowding rare, the children are not naturally protected by subclinical infections caught when they are young and least likely to become paralysed. They therefore remain dangerously susceptible to the virus.

On the other hand, in communities where hygiene is rudimentary and where children contract subclinical infections at an early age and are also carriers of other enteric viruses, these "wild" viruses may prevent effective antipoliomyelitis vaccination with the live vaccine.

The question of the interference of enteric viruses with the polioviruses, and of interference between the polioviruses themselves and how to overcome it, are among the subjects that still require wider study. What was clear from the Washington conference, however, was that in trials of the live vaccine made so far, nothing had arisen to suggest that it was not harmless or to throw doubt on its effectiveness, once the organism had responded to it.

W.H.O. Appointment

Dr. L. G. Eddey has been appointed Area Representative in India of the World Health Organisation.

Dr. Eddey has had more than 30 years' experience in public health work. He was Director of Medical Services and later Chief Medical Officer to the Ministry of Health, Gold Coast (now Ghana). Before that he had served as Director of Medical Services in British Guiana. He joined WHO in 1955 and served in Nepal as a public health specialist.

As Area Representative in India, Dr. Eddey will advise the Regional Director of WHO on the development of schemes of WHO assistance to the country. He will cooperate with the Ministry of Health in working out from year to year a co-ordinated WHO-assisted programme. He will also co-ordinate the activities of the 70 WHO workers in projects throughout India.

Proteins from Grass

Pirie and other scientific workers have directed attention to reserves of protein available in grass and other chlorophyll-containing material normally consumed as animal foodstuffs, but potentially of use to man. The efficient production of good-quality edible protein from such sources depends on the solution of various biochemical engineering problems which have been investigated by the Rothamsted group for some years. A recent report from British Glues and Chemicals, Ltd., reflects the increasing interest in leaf protein. The report states that 100 tons of fresh grass (of 80 per cent water content) yields about 2¼ tons of edible protein together with two important by-products—7 tons of fibre (suitable for the production of hardboard) and 0·6 tons of a 'chlorophyll syrup' containing fat-soluble vitamins, pigments and steroids. The commercial development of this process will be watched with interest by all who are concerned in any way with the nutritional problems of tropical and other areas, and it is to be hoped that the method can be introduced into those regions where additional supplies of supplementary protein are most needed. (*Nature*, March 26, 1960).

International Congress of Histochemistry and Cytochemistry, Paris

The First International Congress of Histochemistry and Cytochemistry will be held at Paris on August 28—September 3, 1960. It is organised under the auspices of the Societe Francaise d'Histochimie, in collaboration with the histochemical societies in existence all over the world. At the Congress, many of the most illustrious names of the world's histochemists will be present. Professor Jean Verne (France) will preside.

Humboldt-Universität zu Berlin, Medizinische Fakultat (Charité)

The celebration of the 250th anniversary of the Charité will be held in Berlin from November 6 to November 10, 1960 in connection with the 130th anniversary of the Humboldt University.

Applications for participation are to be directed to the Committee for the Preparation of the 250th anniversary of the Charité, Berlin N 4, Schumannstrasse 20-21, c/o Dozent Dr. med. habil. Dagobert Müller, secretary of the committee.

Modern Health Hazards

Man is rapidly making the world such an unhealthy place to live in that a whole new approach to public health problems may be needed.

A major new division in the U.S. public health service is being planned to deal with the poisoning of the air, water and food supply that has accompanied 20th century progress, American Surgeon-General Leroy Burney says.

The size of the problem and the inadequacy of existing procedures for coping with it were underscored at a recent hearing before a House of Representatives appropriations sub-committee.

The principal areas explored by a dozen expert witnesses were water and air pollution, radiological hazards, traffic accidents and the use of chemicals in food, drink and agricultural processes.

Regarding air pollution, the number of cars has risen in 50 years from 1,000 to 70 million. In the only city where the situation has really been studied—Los Angeles—it has been found that 3,400,000 pounds of hydrocarbons are being poured into the air each day.

Looking back at the course of events, one witness, Dr. Rolf Eliassen, a professor in sanitary engineering at the Massachusetts Institute of Technology, observed: "Basically, I feel the forces of destruction which are brought about by man and his activities are exerting a greater influence on the environment today than the forces of restitution which man is applying.

Library of the Directorate General of Health Services New Delhi

The library of the Directorate General of Health Services has been fully reorganised and is having various books on scientific medicine added to it every month. The Deputy Assistant Director General announces that this library is open to the entire medical profession.

Eradication of Leprosy

The Leprosy Advisory Committee, which concluded its two-day session at New Delhi on April 20, 1960 under the chairmanship of Mr. D. P. Karmarkar, Union Minister of Health, has recommended the establishment of more leprosy control units as well as integration of leprosy work with the existing health services during the Third Five-Year Plan period.

The Committee noted that the allocation for the leprosy control scheme in the Third Plan was likely to be of the order of Rs. 7 crores, and laid down the outlines for its utilisation. It suggested that leprosy control work should be considered a part and parcel of the general routine work of existing medical and health services, the committee also suggested that voluntary organisations should be encouraged to undertake control work.

The Committee recommended that high priority should be given during the Third Plan for training of medical and para-medical personnel.

The Committee accepted the report of the Sub-Committee on rehabilitation of leprosy patients. It also adopted the scheme of the Hind Kusht Nivaran Sangh for health education involving the preparation of pamphlets, film strips and other material for doctors, paramedical personnel and patients.

The Committee also reviewed the progress of the Leprosy Control Scheme and noted that 101 centres were functioning up to the end of December 1959.

Observers from the State Governments including the State leprosy officers placed before the committee certain difficulties experienced by them in running these units. The Committee examined these difficulties and made suggestions to resolve them.

Shortage of Lady Doctors and Nurses

Tentative estimates of the requirements of women workers of various categories during the Third Plan period have been worked out by the Planning Committee.

According to a study completed by the Planning Commission, the anticipated shortage of lady doctors during 1960-61 and 1965-66 will be 3,220 and 4,360 respectively Men doctors cannot meet this shortage because an overall shortage of 7,000 and 5,000 doctors in 1960-61 and 1965-66 respectively is expected.

The anticipated shortage of lady doctors will be more in 1965-66 than in 1960-61.

The anticipated shortage of nurses by the end of the Second Plan will be about 3,300. This is likely to diminish in 1965-66 to 1,400. Huge shortage of midwives and auxiliary nurse midwives is feared during the Third Plan period. To overcome this the Commission has suggested that immediate steps be taken to open adequate number of training institutions and wherever possible, the number of admissions in training centres be increased.

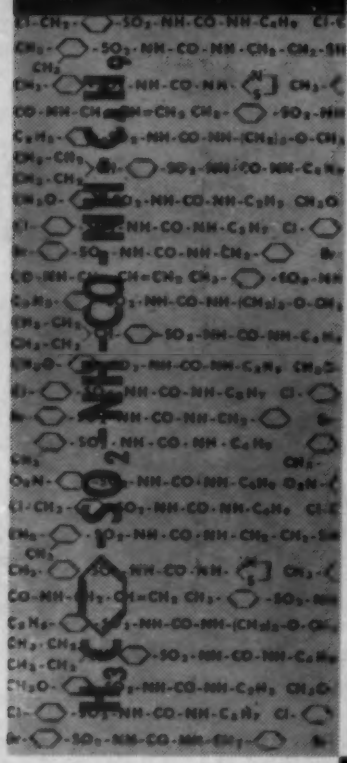
University College of Medicine, Calcutta University

Applications are invited from Medical Graduates of this University or of any other University recognised by this University with special qualification as noted below for admission to the Diploma Course in Dermatology: (i) Completed two years' continuous practice of Medical profession, or (ii) Worked as House Officer for at least 6 months in the department of Dermatology in a hospital recognised by the University, or (iii) Worked as a House Officer for one year in a Hospital recognised by the University.

Applications are also invited from Medical Graduates of this University or of any other University recognised by this University who have at least two years' Postgraduate experience, including house appointments in a general medical and/or surgical wards of a recognised hospital for one year, for admission to the Diploma Course in Medical Radiology and Electrology.

Application forms and other necessary information will be available from the office of the Secretary, University College of Medicine, Darbhanga Building, Ground Floor, Calcutta. Application must reach the Secretary on or before 14th May, 1960.

Facts and Figures



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Health Conditions in India in February

Based on the available data, the preliminary registered birth and death rates in respect of towns with a population of 30,000 and over during January, 1960 were of the order of 20·0 and 10·7 per thousand of population, respectively as against 34 and 12 during December, 1959.

According to the information available the country remained free from plague. Smallpox and cholera, however, continued to be reported from some districts.

The information given below is based on preliminary weekly reports received up to the week ended February 20, 1960.

Cholera: Mild incidence prevailed throughout the month in the districts of West Godavari and Krishna in Andhra Pradesh. Mild incidence was reported from Guntur district in Andhra Pradesh and Puri district in Orissa during the third week of the month. Mild incidence was also reported from Midnapur and the Calcutta city during the first week.

Smallpox: Considerable incidence was reported from Kamrup district of Assam and the Madras city during the third week. Mild incidence prevailed throughout the month in the districts of Guntur, Nellore and Chittoor in the Andhra Pradesh; Nowgong district in Assam; Hazaribag district in Bihar; Poona, Satara South, Amraoti and Greater Bombay in Bombay State; Chhindwara district in Madhya Pradesh; Tanjore, Tiruchirapalli, Madurai district in Madras State; the districts of Bijapur, South Kanara, Kolar, Mandya, Belgaum and Dharwar in Mysore State; Dhenkanal and Kalahandi districts in Orissa State; the districts of Allahabad, Bijnor, Hardoi and Lucknow in Uttar Pradesh; Burdwan district of West Bengal; and Pondicherry.

Mild incidence was reported from Warrangal district in Andhra Pradesh, Ahmedabad district in Bombay State; Salem district in Madras State; Bangalore district in Mysore State, Balasore, Keonjhar and Koraput districts in Orissa State and the districts of Banda, Kanpur, Etah and Meerut in Uttar Pradesh during the third week.

Kyasanur forest disease: During the week ended February 20, 1960 a total of 10 human cases and 10 deaths among monkeys were reported from Shimoga district of Mysore State as against 7 human cases and 18 deaths among monkeys, respectively reported during the week ended February 13, 1960.

Gastro-enteritis: 22 cases and one death were reported from Lucknow and Varanasi districts in Uttar Pradesh during week ended February 20, 1960. During the week ended February 13, 1960 only 6 cases were reported as against 4 cases during the previous week.

Influenza: During the month, 30 cases were reported from Jhalawar district of Rajasthan. Stray cases were also reported from Assam, Bombay and West Bengal.

Findings of National Tuberculosis Survey in India

The National Tuberculosis Survey has revealed that about 5 million of India's population is suffering from pulmonary tuberculosis. The number of infectious cases is about 1·5 million.

The statistics also indicate that the prevalence of tuberculosis is higher among higher age groups than among younger ones. The number of women affected by tuberculosis is in general less than that of men. This difference is specially marked in the higher age groups.

The importance of socio-economic conditions and environmental factors has been emphasised by the finding that people living in kutcha houses were more prone to the disease than those living in pucca houses.

The report says that the differences, if any, in morbidity rates between towns, cities and villages are much smaller than was earlier expected. The incidence of tuberculosis in rural areas is generally lower than in cities and towns but the difference is not marked.

The survey was conducted by the Tuberculosis Sub-Committee of the Indian Council of Medical Research. Dr. P. V. Benjamin, Tuberculosis Adviser to the Government of India, was the Chairman of the Sub-Committee. The survey was started towards the end of 1955 and completed early in 1958.

The Survey was limited to investigations on pulmonary tuberculosis, one of the most important forms from the epidemiological and public health points of view.

Various types of population in selected cities, towns and villages in the States of West Bengal, Bihar, Uttar Pradesh, Delhi, Punjab, Andhra Pradesh, Mysore, Madras, Bombay and Kerala were covered by the Survey. About 3,00,000 persons were examined in six cities, 30 towns and 151 villages.

The groups included in the Survey were chosen in accordance with statistical principles so that the findings might be of general application. Six institutions were entrusted with the Survey work. These were: the Tuberculosis Centres in New Delhi, Patna, Hyderabad and Trivandrum, the All India Institute of Hygiene and Public Health, Calcutta, and the U.M.T. Sanatorium, Madanapalli, Andhra Pradesh.

The entire population, excluding children under five years, in the areas selected for survey was subjected to mass miniature x-ray examination and, those suspected, to further bacteriological tests.

CORRESPONDENCE

The Editor is not responsible for the views expressed by correspondents

India and the International Congress of the History of Medicine

SIR,—Inspite of much talk about promotion and propagation of Indian culture abroad, and deputing cultural delegations to foreign countries, there is a lack of interest, if not ignorance and apathy, regarding History of Medicine in India and abroad.

Four years ago, a question was asked in the Rajya Sabha "whether India has invited the International Congress of History of Medicine", and the Director-General of Health Services, in his letter No. 18-57/56 dated 4-8-1956, requested me to furnish some informa-

tion about the aims, objects and activities of the above organisation.

During the last decade, the Congress was held in the following countries:

1952—XIII International Congress of History of Medicine in France (in Nice), September 1952.

1954—XIV International Congress of History of Medicine in Italy (Rome and Florence), September 1954.

1956—XV International Congress of History of Medicine in Spain (Madrid and Salemanca), September 1956.

1958—XVI International Congress of History of Medicine, was expected to be held in Great Britain, but was subsequently arranged in France (Montpellier), September 1958.

The organisers of these congresses have been extending invitations to various countries and national associations of history of medicine, universities, medical colleges and individuals, to send delegates and to participate in the congress. But, for various reasons, India has not been able to send, till now, any delegation or even one official delegate to the congress, although 30 to 50 countries and nations send their delegates to each International Congress of History of Medicine. This year, in September 1960, the XVII International Congress of History of Medicine is to be held in Greece (Athens and Cos) and circulars and notices have been received in India.

Usually, for such international congresses, it is the learned institutions like academies, professional societies, research associations, universities and faculties, which send delegates to represent a country or a nation. In India, however, except the Indian Association of History of Medicine, there is no scientific or professional associations which is primarily interested in the history of medicine. Probably, the Asiatic Society (Bengal) and the National Institute of Sciences, may take some interest in such congress. Some of the older universities, with strong faculties of history and oriental learning, side by side with medicine, may have developed some contacts with the history of medicine. It is, therefore, necessary that the Ministry of Health, Government of India, U.N.E.S.C.O., South East Asia Regional Office, the Rockefeller Foundation and the Ministry of Culture and Scientific Research, should take a little more interest in the matter and encourage medical historians and other scholars to represent India at the next congress, present papers on behalf of India, and focus attention to our contributions and achievements in the field of Public Health and Medicine. Adequate inducements in the form of travel grants, fellowships and official delegations should be generously offered immediately, so that India is properly represented at the forthcoming congress in Athens in September 1960.

The necessity of sending a representative delegation or delegates to this Congress is imperative, particularly on account of the fact that even before and specially after the visit of Alexander the Great to India, there was considerable intellectual intercourse between Greece and India. This is evidenced by the similarity of philosophical systems or medical theory and practice of both the countries in ancient times. It is only by a close personal contact and 'on the spot' study that many of the problems concerning the inter-relations between ancient Greece and Hindu Medicine can be satisfactorily understood and appreciated by scholars in India. The presence of an Indian delegation at the congress in Greece, will, in turn, stimulate the European and American scholars, to obtain first-hand knowledge of the History of Medicine in India, by visits and study tours to India. India, being one of the earliest cradles of civilisation and one of the earliest centres for the evolution of the art and science of medicine, should not go unrepresented at the forthcoming congress. It is our duty to see that our heritage in Health and Medicine is not cast into oblivion, because of the ignorance of nations newly born, and the neglect of our own nation.

It is not too much to expect that Indian scholars, medical men, politicians and administrators will appreciate the value of promoting historical and cultural aspects of medicine by inspiring the coming generations of India, and bringing about a better understanding between nations of the East and West, and creating the concept of 'One World' and 'One Medicine'. I am etc.

D. V. Subba Reddy

Director & Professor

Upgraded Department of History of Medicine

Osmania Medical College, Hyderabad—A.P.

Problems of Licentiates*

Sir,—I have read Dr. S. Bhattacharjee's views on the problems of licentiates in your Journal (**34**: 7, Jan. 16, 1960) with a great deal of disappointment.

Dr. Bhattacharjee seems to have no other solution to offer to this problem than private practice for the licentiates. But why only private practice and why not all the normal pursuits of a medical man in all spheres? My appeal, therefore aims at removal of obstruction, thereby enabling the licentiates to take their rightful place in common with every one of the profession with proper opportunity for progress and development. It should be easy enough at this stage because all our national leaders, particularly our Prime Minister, have recognised the evil of casteism and denounced its continued existence in any form or manner.

When M.B.B.S. as the minimum standard of basic medical qualification for the profession has been laid down and accepted, I can only advocate that the licentiates should try to equip themselves with that qualification. The authorities concerned should also be alive to this fact and open all the facilities to licentiates accordingly. There is nothing derogatory to ourselves in this nor is there any asking for mercy or for crumbs. I am etc.

Dhakuria,
12-2-'60.

A. C. Sen Gupta.

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* Further correspondence on the subject under discussion will not be entertained.—Ed., *J. Indian M. A.*

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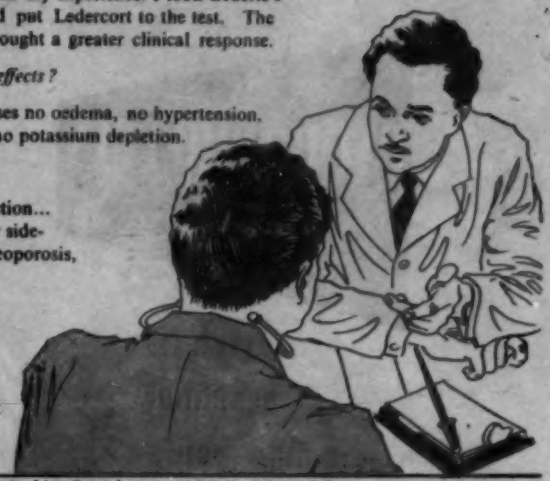

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REVIEWS

Medical Annual 1959, 77th issue—Editors: R. Bodley Scott, M.A., D.M., F.R.C.P. and Milnes Walker, M.S. (LONDON), F.R.C.S.; John Wright & Sons Ltd., Bristol; 8½" × 5½"; pp. xl+620; price 40s. net.

As in previous years the Annual contains a few special articles on current topics besides a general review of the year's work. The excellent articles on newer progesterones by Dr. Bishops deals elaborately with the recent development in this interesting subject Two other medical articles on two common subjects, one on cross infection and the other on emphysema are quite interesting. The growing importance of fluid and electrolyte balance has been focussed in this issue of the Annual, though belated. The recent trends in the field of cancer research has been briefly and lucidly discussed by Dr. Haddow.

The rest of the book gives the important development in the various branches of medicine for the busy general practitioner. The selection of the subjects though very widely done, is to some extent dependent on the liking of the contributors. It is inevitable that such an annual review of all the different branches of medical science can hardly be very comprehensive or up-to-date. The section of pharmacology is very poorly represented. So also is the section on tuberculosis, where a sketchy report of a local development can only interest the local practitioner of Great Britain.

However the volume, as in the past, will be eagerly consulted by practitioners all over the world and surely they will be rewarded with the rich and accurate information about the recent development in various disciplines of medical science.

H.S.C.

Pocket Medicine—By G. E. Beaumont, M.A., D.M. (OXON.), F.R.C.S., D.PH. (LONDON). 1959, 4th Edition; J. & A. Churchill Ltd., London; 7½" × 5½"; pp. 212; price 12s. 6d. net.

Personally I do not encourage students going through 'note books' as I feel that note books lack thoroughness. The volume under review is an exception. It is a treasure which can be carried anywhere. For the final year students it is a boon. General practitioners can use it as a handy reference book. It has been well printed and nicely produced.

S. K. MUKHERJEE

Disinfection and Sterilization: Theory and Practice—By G. Sykes, M.SC., F.R.I.C. E. & S. Livingstone Ltd., Edinburgh 1; 9¼" × 6"; pp. xxiii+396; price 75s. net.

This book is a treasure of information regarding various methods of sterilisation. The frank expressions about different methods of sterilisation used by experts are of considerable value. The English is simple and the diagrams are quite explicit in explaining the functions.

It is worth keeping in all medical libraries as a reference book.

M. MUKHERJI

Arterial Embolism in the Limbs—By A. L. Jacobs. 1959, 1st Edition; E. & S. Livingstone Ltd., 16, 17 Teviot Place Edinburgh; 10" × 7"; pp. 220 with index; price 35s. net.

Monographs come in two forms. One depicts the personal experience and study, often of a lifetime, of a certain subject; the other is often a collection of the material from the literature with a view to evaluate the basic picture of a particular condition. Both may be masterly in form; only one provides a maturity of opinion. For sixteen years Dr. Jacobs has been studying the clinical and anatomical material in 122 incidents of limb embolism, 48 of which have been followed to autopsy. Their analysis has been studied against the background of a further 269 old arterial occlusions in cases of mitral stenosis. With the support of experimental and arteriographic observation of anatomical collaterals after embolism, the author has produced a true monograph on his subject. Commendable also is the restraint advocated in the management of these lesions. Over sixteen years, this long study has watched and weathered the evolution of management of the embolism from the gloom of days gone by to tempering the wave of enthusiasm in embolectomy, except for occlusion of the larger limb arteries. Excellent studies portrayed in the experimental section would make ideal starting points for teaching experimental surgery students the problems of collateral circulation and its development.

The book is very moderately priced, has the Livingstone finish about it, and makes valuable study for all concerned with the clinical appraisal, anatomical understanding and careful management of the arterial embolism in a limb.

GODREJ S. KARAI

Pädiatrischer EKG-Atlas—Von Priv.-Doz. Dr. W. Heck und Dr. J. Stoermer, Göttingen. Mit einem Geleitwort von Prof. Dr. G. Joppich, Göttingen. 1959. XVI, 230 Seiten, 181 Abbildungen in 228 Einzeldarstellungen und eine Messtafel zur Bestimmung des Vektors und zur Ausmessung der Herzfrequenz, Lex.-8° (Georg Thieme Verlag, Stuttgart), Genzleinen DM 78.

Paediatric ECG-Atlas—By Priv. Doz. Dr. W. Heck and Dr. J. Stoermer, Göttingen, with a foreword by Prof. Dr. G. Joppich, Göttingen (In German). XVI, 230 pp., 181 illustr. in 228 figures and a table for finding out the vectors and measuring the heart rate. Georg Thieme, Stuttgart, 1959. DM 78.

Paediatric cardiology has assumed unexpected importance due to the development of cardiovascular surgery. Apart from angiocardiography and heart catheterisation, the electrocardiogram is the mainstay among diagnostic methods. New leads, vector cardiography, etc., have increased its usefulness and accuracy.

The peculiarities of infancy and childhood have their own margins of normal values which has to be established, a task in which the present authors took active part. The work under review is based on a great number of their own cases, observed at the Paediatric, Medical and Surgical University Clinics, Göttingen. The general part contains, apart from introductory remarks on the E.C.G. and vector cardiogram of children, a large amount of normal time values, arranged in 16 tables according to age from 0 to 14 years. The atlas proper consists of the E.C.G.s of 161 different cases, normal and pathological; many of them have been traced serially, before and after medical or surgical treatment, etc. Some are accompanied by x-ray photographs of the heart and all by detailed clinical and E.C.G. findings, clinical and, when available, post-mortem or operative diagnosis. These legends are so well done that they give a vivid and exhaustive picture of every case. The E.C.G.s cover every conceivable clinical condition so that they represent a complete pictorial textbook of paediatric cardiology. A translation in two or three languages could be easily carried out, the text being short, and could be a most welcome addition to paediatric and cardiologic literature.

ROBERT HEILIG

Die cerebrale Gefässsklerose : Diagnose, Behandlung und soziale Aspekte—Von Prof. Dr. H. E. Kehrer jun., Münster/W. 1959. VIII, 238 Seiten, 17 Abbildungen und 4 Tabellen, 8°, (Georg Thieme Verlag, Stuttgart), flexibles Ganzleinen DM 28.

Cerebral Vascular Sclerosis : diagnosis, treatment and social aspects—By Prof. Dr. H. J. Kehrer, Münster/W. VIII, 238 pp., 17 illustr., 4 tables, (in German). Georg Thieme, Stuttgart, 1959. DM 28.

The author put himself the task to consider this disease, which is spreading in highly developed countries, not only in the manner of a textbook chapter but from all practical aspects. Arteriosclerosis of the cerebral vessels has been here treated from the general medical, the neuropsychiatric and, particularly, also from the social point of view. Because of the fact that this cerebral disease affects equally bodily functions and mental behaviour, the author analyses in detail the manyfold psychosomatic inter-relations which this syndrome presents. Diagnosis and differential diagnosis have also been discussed from the somatic as well as from the psychologic angle, separating the limited facilities of the consulting room from the elaborate methods available at the clinic. The voluminous literature of cerebral circulatory disturbances has been critically sifted; older publications have been partly excluded in favour of more recent ones; particularly such that contain many references. A comparatively large part has been devoted to describing numerous promising methods of treatment and prevention. A special feature of this monograph is the detailed discussion of the social problems arising from sclerosis, including expert opinion on legal responsibility of and care for such patients. Chapters on the role of this disorder in family life, in history and literature conclude this stimulating addition to such books that are interesting not only to the medical but also the legal practitioner and all those who have to deal with medico-social questions of today and tomorrow.

ROBERT HEILIG

Beschäftigungstherapie : Einführung und Grundlagen—Herausgegeben von Priv.-Doz. Dr. G. Jentschura, Heidelberg. Unter Mitarbeit von H. Gardemin, Hannover, F. Hillers, Ilten/Hannover, H. W. Janz, Ilten/Hannover, G. Jentschura, Heidelberg, W. Langer, Rotenburg/Hannover, E.-M. Rudel, Heidelberg, W. Wigand, Hannover. 1959. VIII, 300 Seiten, 125 Abbildungen, Gr.-8° (Georg Thieme Verlag, Stuttgart), Genzleinen DM 45.

Occupational Therapy : Introduction and Principles—Edited by Priv. Doz. Dr G. Jentschura, Heidelberg, with 6 collaborators. Foreword by Prof. Dr. K. Lindemann, Heidelberg (in German). VIII, 300 pp., 125 illustr., Georg Thieme, Stuttgart, 1959. DM 45.

The increasing importance of occupational therapy (o. th.) has been recognised in Germany by legislation, as a consequence of which 3 schools have been started for the training of occupational therapists. Their status found international recognition by affiliation of their association to the World Federation of Occupational Therapists in 1958. The present work has been planned as a text-book for therapist students but it also shows to doctors concerned what help they can expect from this fairly new therapeutic technique. The first 60 pp. with 58 illustr. give a general survey of the various crafts used in occupational therapy such as weaving, tying of knots, bobbin- and raffia-work, book-binding, pottery, leather-, wood-, bone-, coconut- and metal works, textile printing, household work and self-help in daily life. Then follow chapters on o. th. in orthopaedics and accident treatment (82 pp., 32 illustr.); functional o. th. (30 pp., 24 illustr.); o. th. in tuberculosis patient (42 pp, 11 illustr.), and an excellent introduction (76 pp.) to o. th. in psychiatry.

The authors of this well produced treatise have been fully successful in their attempt to produce not only a useful guide to the study of their subject but also to show the manifold and decisive help which o. th. can give in the rehabilitation of numerous disabilities.

ROBERT HEILIG

Klinik und Praxis der Urologie : Klinik, Indikation, Diagnostik, operative und instrumentelle Eingriffe, Nachbehandlung. In zwei Bänden—Von Prof. Dr. W. Staehler, Tübingen. Mit einem Geleitwort von Prof. Dr. Th. Naegeli, Tübingen. Band II : XXII, 863 Seiten, 641 teils mehrfarbige Abbildungen, Lex.-8°, (Georg Thieme Verlag, Stuttgart), Ganzleinen DM 240. Mit Sach- and Namensverzeichnis für Band I and II. Der Bezug von Band I (erschienen im Juli 1959) verpflichtet zur Abnahme von Band II. Prtis des Gesamtwerkes DM 480.

Clinic and Practice of Urology—By Prof. Dr. W. Staehler, Vol. II; pp. 863 with 641 partly coloured illustr.;

authors' and subject index for vols. I & II (in German). 1959, Georg Thieme, Stuttgart, DM 240. Price of both vols. DM 480.

The second volume is divided in two main parts, a medical and a technical one. The former (190 pp.) deals with anuria; nephritis, ischaemic (surgical) hypertension, circulatory disturbances, haematuria; injuries, fistulas, foreign bodies, parasites and expert opinion, and, finally, with disturbances of male sex functions.

The technical section is subdivided into diagnosis and treatment. Examination of the patient, and of the excreted body fluids; blood chemistry, function tests; technique of radiological examination, x-ray diagnosis and differential diagnosis; and cystoscopic diagnosis are all dealt with in sufficient detail and, yet, concisely. For the urological surgeon, of the greatest interest are the next 300 pages that under the heading "therapy" give clear and copiously illustrated instructions on anaesthesia; cystoscopy and catheterisation; operative cystoscopy; operative technique; plastic operations on the bladder; dangers and complications during and after operations. A supplement discusses prevention and treatment of thrombo-embolism, and the artificial kidney. The authors' index fills 15, the subject index 189 pp. and seems a model of completeness. All the praise given to the first volume holds good for the whole work. It is simply amazing how one man, except for the supplement, could produce such a monumental work, treating every section of this vast subject with equal competence. The perfection of production needs hardly to be mentioned.

ROBERT HEILIG

Medizinische Grundlagenforschung—Beirat: K. Bucher, Basel, W. Doerr, Kiel, A. Grumbach, Zürich, N. Henning, Erlangen, H. Holzer, Freiburg/Br., A. Kornmüller, Göttingen, J. Kühnau, Hamburg, H. Schaefer, Heidelberg, H. Schoen, Göttingen. Herausgegeben von Prof. Dr. K. Fr. Bauer, Erlangen. Band II —Bearbeitet von Zahlreichen namhaften Fachgelehrten des In- und Auslandes. 1959. VIII, 827 Seiten, 187 Abbildungen, 63 Tabellen, Lex.-8°, (Georg Thieme Verlag, Stuttgart), Ganzleinen DM 168.

Medical Fundamental Research—Editor Prof. Dr. K. Fr. Bauer, Erlangen, Vol. II: Contributions by numerous renowned German and foreign experts (in German). VIII, 827 pp., 187 illustr., 63 tables. Georg Thieme, Stuttgart, 1959. DM. 168.

The 17 articles have been written by 28 research workers from Germany, Switzerland, France, Austria, Italy, Denmark, Sweden and the U.S.A., each of them covering subjects to which he or she made original contributions. The titles will show what a wide range they cover. Pain, protective system and morphine-like acting substances; descending influence of the retecular formation; physiology of vegetative nerve centres; cytology; fibrinolysis; advances in arthrosis—arthritis research; pathology of endocarditis; morphological manifestation of external and internal O_2-deficiency; biochemistry of inflammation; cancerogenic substances; chemotherapy of tumours; advances in chemotherapy of skin diseases; cell electrophoresis; vitamin B_{12}-analogues; development of structure in nature and the Second Fundamental Principle of Thermodynamics. Most of the sections are too technical for the practitioner or clinician; but for specialists in the respective subjects they are of the greatest value, as they are giving the most recent *avant-guarde* positions of fundamental research. References in many languages are so numerous that the literature of the various subjects seems to be completely covered. The illustrations are of the highest quality. This publication deserves the highest praise.

ROBERT HEILIG

Care of the Surgical Patient—By Jacob A. Glassman, M.D., F.A.C.S., F.I.C.S. and R. W. McNealey, M.D., F.A.C.S., F.I.C.S. 1959, Williams & Wilkins Co., Baltimore, Maryland, U.S.A.; 9" × 6"; pp. 320; $6·50.

It is quite an instructive book dealing with the preoperative and postoperative care of surgical patients. It will be of great help to house staff as well as to surgeons.

SUBRATA BANERJEE

OBITUARIES

Dr. C. J. Mehta

Dr. C. J. Mehta was born on 14th August 1930. He qualified as an M.B., B.S. in 1952 and worked as a pathology externe, house physician and research assistant (anaemia) at the Municipal General Hospital, Sion, during 1953-54. He also worked as medical officer, Hindu Deen Daya Sangh. He was an associate editor, *Journal of the Indian Medical Profession* during 1954. In 1953 he set up practice at Sewree.

Dr. Mehta inaugurated the Infants Healthy Scheme in the Government Housing Colony, Sewree, in 1956 and started another dispensary at Chembur in October 1959. He became a panel doctor under the E.S.I. Scheme. He gained popularity among all classes of patients particularly industrial workers. He was a keen sportsman.

Dr. Mehta was an active member of the Bombay Branch, I.M.A. He expired on 21-12-59 in the Lokmanya Tilak Hospital.

Dr. Mrs. Dossibai J. R. Dadabhoy

Dr. Dossibai J. R. Dadabhoy passed away suddenly on 16th January 1960 due to an attack of coronary thrombosis.

Born on 16th October 1881 of a wealthy family in Bombay, she received very liberal schooling. She joined the Grant Medical College graduating in 1903. In 1907 she joined the Royal Free Hospital and School of Medicine for Women in London and signed up for M.D. in 1910. She was the first and only woman candidate to appear for L.R.C.P. and M.R.C.S. examinations which

DR. DOSSIBAI J. R. DADABHOY

DR. C. M. TRIVEDI

DR. B. N. MAHEY

she passed creditably. She was the first woman to get her M.R.C.P. after a couple of years. In 1912 she qualified as an M.D. of the London University and returned home as the first Indian woman doctor.

She married Mr. Jehangir Ratanshaw Dadabhoy, an engineer, in 1915. She started her practice in Bombay as an obstetrician and gynaecologist. Her subjects of particular interest were functional haemorrhages and malignancy.

She was the first Honorary Obstetrician at the B. D. Petit Parsi General Hospital. She was efficient both as a practitioner and a teacher. She contributed a few papers on her work with radium.

Dr. Mrs. Dadabhoy was the first woman doctor to join the Indian Medical Association and rose to the Presidentship of the Bombay Branch of this organisation in the year 1941-42. She was also elected Vice-President of the Indian Medical Association at the Centre. She was President of the Association of Medical Women in India. A founder member and one responsible in starting the Bombay Obstetric and Gynaecological Society, she worked as Hony. Jt. Secretary for a number of years and largely contributed to the formation of the Federation of Obstetrics and Gynaecological Societies of India. She presided in 1955 over the 8th All-India Obstetrics and Gynaecological Congress. Earlier, the then Government of India invited her to serve on the Health Survey and Development Committee known as Bhore Committee. During the war years, she worked on the Bombay Branch of the Red Cross Society. It was through her efforts that blood transmission service was started in Bombay by the Red Cross Society.

In appreciation of her work the Government awarded her M.B.E.

Her hospitality and generosity are well known. Her recent donation of Rs. 20,000/- to the Silver Jubilee Fund of the Bombay Obstetric and Gynaecological Society speaks of her munificence.

She was a staunch nationalist, disregarded foreign clothes, and put on only the Indian made fabrics till the last day of her life.

Dr. C. M. Trivedi

Dr. Champaklal Trivedi was born and educated at Karachi. He had his medical education at the Grant Medical College, Bombay. After qualifying he started practice at Mulund. Soon after he shifted successively to Dadar and Khar in 1943. He was also an industrial medical officer to the Bombay Port Trust. He went to Japan twice for special training in family planning and birth control and on his return shifted to Colaba. He was a panel doctor under the Employees' State Insurance Scheme and his sympathetic approach made him very popular amongst workers. He had an attack of coronary thrombosis on 22nd December 1959 to which he succumbed. He was 44.

Dr. B. N. Mahey

Dr. B. N. Mahey was born at Jammu (Jammu and Kashmir State) on January 24, 1904.

After medical studies at Indore which he successfully completed on State Government scholarship, Dr. Mahey joined the Jammu and Kashmir Government service where he continued till the eve of partition of India.

In 1948 he shifted to Rampur State and started independent practice at Civil Lines where he soon endeared himself to all in every walk of life. To have set up a unique reputation in such a small span of time shows the inherent qualities of head and heart that Dr. Mahey abundantly possessed.

Dr. Mahey succumbed to a heart attack on January 30, 1960.

SUPPLEMENT
Journal of the Indian Medical Association

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III ANDHRA PRADESH MEDICAL CONFERENCE, 1960, ELURU

The 3rd Andhra Pradesh Medical Conference was held at Eluru on February 28-29, 1960. Dr. D. Rajasekhara Rao, the Chairman of the Reception Committee extended a hearty welcome to the guests and delegates. In his welcome address, Dr. Rao said inter alia, "Medical facilities here are by no means of low order. There is a big hospital with all the modern facilities, which is sufficient to make a start of a new-type Medical College suitable for the comprehensive health schemes. We are proud of benevolent donors like Sri Mullapudi Harischandra Prasad and other members of his family, who have already contributed a lot in that direction and helped to start a Medical College at Kakinada, a Polytechnic and Maternity Hospital at Tanuku.

Under the rapid changes that are occurring in society to-day, we are beginning to accept new interpretations of the functions of the doctors, their education and their practice, emoluments and obligations to the society and the private practitioner fills an important role in the medical services of the country. As such, no effort should be spared to make him as efficient as possible and he must be given every opportunity to fill up the gap between the Government Medical Officer in the primary unit and the Specialist at a higher level. We hope that the deliberations of this Conference will help to evolve a pattern of health services, which will be workable by the State, with the minimum expenditure but serving the maximum number of people. Otherwise, modern medicine will stand in danger of losing popular support."

Dr. D. Rajasekhara Rao
The Chairman of the Reception Committee

Dr. P. S. Giri, the president of the conference in his presidential address dwelt on the various medical problems of the present day. He said:

"The General Medical Practitioner and also the Family Doctor, form the bulk and backbone of the medical profession. On him devolves the major share of the health load of the Nation. He has been led to believe that his concern is sickness—not health; his duty is to cure and not to prevent disease. But the time has come to reorientate his attitude.

More practical and less costly domiciliary treatment is slowly replacing costly hospital treatment. No one is better fitted for it than General Practitioner. It is, therefore, necessary that he should have diagnostic aids made available at Government hospitals. Experience has shown that with close laison between the general practitioner and the local health authorities domiciliary service can be better organised, more successfully developed and more profitably extended.

As preventive and social medicine are assuming greater importance and form the least expensive of the health machinery, more and more calls are made on general practitioner. He is the person best placed to give effective advice on the maintenance of health including mental health.

70 per cent of the medical profession is constituted of independent medical practitioners. The co-operation and assistance of this large body will be invaluable for the success of various development programmes such as Family Planning, prevention and eradication of Tuberculosis, Leprosy, Malaria etc. The willing co-operation is therefore mere asking; but this has not received due recognition.

College of General Practitioners:

Dr. Karmarkar who was addressing the 36th All India Medical Conference has asked the conference to work out such scheme immediately and assured necessary financial aid and other assistance from the Government. I suggest that there should be one such college in every State. General Practitioners with ten years standing must also be allowed to appear for a Post-graduate Degree.

The Minister observed that the proposed refresher course would be of great value to those who practised their profession away from the big medical centres as

THE CONFERENCE IN SESSION

they were not able to acquaint themselves with the latest techniques very easily. The scheme, if it materialised would go a long way in improving the National standard of health. I am very glad to note that such refresher course lectures are being conducted in our state particularly at Vijayawada under I.M.A. Branch.

Pathological Museum:

Mr. Karmarkar told the conference that the Indian Council of Medical Research was contemplating the establishment of a Pathological Museum for the benefit of medical practitioners working in the interior, and desirous of acquiring advanced knowledge in this branch.

In all faith I appeal to Sri P. V. G. Raju, the Health Minister to take advantage of the offer made by Hon. D. P. Karmarkar, Union Health Minister, and start a "College of General Practitioners", as a pioneering project. It would be a sure and sound method to infuse life into the discriminated and disheartened career of the General Practitioner, and to pool and distribute the medical experience and knowledge, to the needy people at large.

State Health Service:

The State continnes to pin its faith almost exclusively in its services which are admittedly inadequate to the needs of the State and virtually ignore, general practitioners. Medical services are confined to hospitals which besides being far too few are poorly staffed and equipped. One rightly described it as the most expensive and monumental. The modern trend, in better governed countries is to spend more money in keeping patients not in but out of hospitals. Cheaper medicine is preventive medicine. Cheapest medicine is efficient cure of patients in their homes.

In the state health services, morale of the personnel is not as high as it ought to be and this is said to be going down. The reason is that he has little or no hand in the organisation, planning or its results. Another factor is more administrative and political interference. The third reason is, he is denied a 'living wage'. Hence, more frustration, depression and disappointment are fast enveloping the services, especially the younger generation. This needs serious notice and investigation.

You see now, how state health services and general practitioners are interlinked with and depend upon each other for the purpose of prevention and cure, in fact indivisible and inseparable. The administrators should harness the two together, if National positive health is our ultimate goal.

MEDICAL EDUCATION

With the proposed Medical College at Tirupati and with rupees one crore central grant for expansion of medical colleges, our Pradesh will be having eight medical colleges. Therefore, in a near future demands of our medical relief programme can be met to a large extent.

The pattern of medical education still followed in the State is a 'carbon-copy' of the British system. In setting up a pattern, the socio-economic-political and educational "New Dynamics" have to be borne in mind. Wisdom would lie in evolving and adopting a pattern that will suit our state best, keeping in view the international standards.

Pre-Medical Education:

It must be realised that in addition to technical background in pre-medical sciences, a student must also possess a fairly good general and academic knowledge.

Selection of Students:

The existing system needs a revolutionary change. Scholastic ability must undoubtedly be the chief criterion with personal interviews without snags. A notable experiment in selection adopted by the Christian Medical College at Vellore with necessary modification may be applicable to our state.

Curriculum:

The world conference of medical education has agreed to unify and simplify curriculum with a view to reduce memorising a mass of details which stultify thinking and self-education. A beginning however is being made in some states to prune the curriculum without sacrificing the standards.

Teaching:

Lecturing is a legacy of the hoary past, when books were rare and knowledge was largely transmitted by spoken words.

Now that there is a plethora of text books. Lectures have become secondary in importance. They must give place to teaching, how to use books, punctuated with illustrations, slides, comments and brief notes.

One thing in which progress has been scanty is the clinical post-mortems and will continue to be so, unless there is legislation in some form which would make more material available for post-mortem study.

Attempt should also be made to correlate pre-clinical studies more closely with clinical work. This integration is imperative to produce comprehensive medical course. Clinical teachers are specialists and they teach as specialists. This has created a serious problem to students as their clinical experience is fragmented and distorted.

Social Medicine:

Medicine is a profession of social service. Social and Clnical medicine have identical objectives and are kinetic living concepts. The medicine of today and of tomorrow

must be preventive and social. These aspects should become an important part of our training and practice.

Psychological Medicine:

This has rightly come into its own though much belated. It is futile to try to cure the body without curing the mind. General Practitioner should possess a good knowledge of this branch of medicine to handle all psychosomatic disorders.

Additions:

Paediatrics and Mental Health have grown into major subjects. They must be taught and the strain caused by this additional load of instruction can be lessened by eliminating those parts of the curriculum in other branches which have outlived their utility.

Examinations:

They need complete rather revolutionary reorientation. They, as they stand at present, exercise a cramping effect on student's mind hampering the progress of education.

Students are admitted after stiff competition and cannot therefore be below average intelligence. It is also an admitted fact that large number of failures in colleges are due to mass admission and inadequate staff with low bed strength. The examinations should be made much simpler and less exacting at all stages.

Internship:

The training of interns in wards with low bed strength crowded with medical students and house surgeons seldom give satisfactory results. The remedy for this is to upgrade District Hospitals for recognised training of interns.

Post-Graduates:

These degrees in our State are to some extent beyond the reach of many deserving candidates and there seems to be a lot of "selecting" for this. Five years after graduation, every graduate should be entitled to sit for a post-graduate degree and there should be no arbitrary impediment.

Post-graduate education has made some progress in recent years, but attention has so far been directed to the production of teachers and specialists. Refresher Course Lectures conducted at various general hospitals in our State is a step in the right direction.

Research:

The prizes of private practices produce a great economic disparity between doctors engaged in research and in successful practice. This is to a great extent responsible for the poor progress of our medical research. It is therefore necessary that our research men should be generously compensated. His status and promotion should be determined by his scientific achievements and not the number of years on Government pay rolls.

Professorial appointments should be the reward of sustained scientific labours and accomplishments. In our State there is a wealth of clinical material for research. Every teaching hospital should have a research unit with all facilities. (Great research scholars like Osler and others had their inspiration from general practitioners with rich clinical experience). The general practitioner must be encouraged to do research work in clinical and social medicine and should be rewarded by the government for producing standard results.

Drug Industry

Pharmaceutical industry is the crying need of the day in India. The pharmaceutical enquiry committee found that there are 1700 factories in India manufacturing pharmaceuticals, but only 100 of them are worth the name.

Our pharmaceutical industrialists have hitherto been concerned with manufacturing hybrid combinations of

Dr. P. S. Giri
The President of the Conference

indigenous and the so called allopathic drugs, giving them catching and attractive names. This is not the industry we want. Drug industry should develop, organise and exercise influence on the medical profession by helping research conducted in pharmacology and therapeutics in any University.

The industry, medical and pharmaceutical profession and Government should consider ways and means of limiting the present proliferation of the poly-pharmaceutical preparations and the firms should be encouraged to take up genuine research. It is admitted to be impossible for any practitioner to familiarise himself with details of new developments in all branches of medicine. In America since 1959 a monthly "Medical Letter" on "Drugs and Therapeutics" is being published with the aid of distinguished medical advisers wherein the evidence for and against a drug is stated and evaluated. Good drug firms should welcome this development for, in the long run dissemination of reliable information of their products is sure to benefit them. The need for a publication like this "Prescribing Journal" is a real and urgent need, for a busy practitioner and has to be financed by the drug industry.

Drug Act:

The Act was well meant but in actual working it has failed to achieve its objectives due to lack of supervision and inherent lacunae. The spurious and adulterated drugs are being sold on a fairly large scale. The Act and its rules work severely on Medical Practitioner, but there is no check on quacks and patients.

I hope that our Pradesh Government will soon extend and enforce the Drug Control Act to Telangana area for uniform control. A confusion would not occur to the profession if the drugs were sold under their pharmaceutical names and not under trade names. I suggest that a provision should be made in the law. Those who violate standards, should be ruthlessly weeded out. Panicky restrictions of imports should have no place in the case of life-saving potent drugs and precision instruments.

Population, Food and Planning

The population in India is growing fast. According to Census Commissioner the number in 1983 will in the ordinary course of things reach the level of 52 crores unless of course, there are famines and pestilences. The continuously ascending spiral of the country's population seems to undo our planning. Scientific development of agriculture, might offer some cure but it cannot absorb all.

Family planning has come to stay as an integral part of our planning. All Government expenditure in implementation of suitable birth control schemes will be an investment.

There are about 100 centres in Andhra pradesh, where family planning information is given. They do not even touch the fringe of the problem. Family planning information is sought from the trusted and intimate family doctor and therefore, every general practitioner is the right vehicle to impart this knowledge hence, the services of the general practitioner should be mobilised.

Unless the message reaches the lowest economic strata of the community which is really most profile, population control will not be effective.

Another essentiality is intensive research work which can place cheap and easy oral contraceptives within the reach of an average man. Planning the family, aims also at having the wanted child with an environment conducive to health and happiness of the family. If adequate development of the child has to be ensured, the pregnancy should be undertaken at well spaced-out intervals. Spacing of children provides a measure of safety towards preserving the health of the mother and care of the child.

Our Union Health Minister has promised to give a sizable grant to I.M.A., if it could organise one. I.M.A. has already submitted a scheme to Government of India and I hope it will be accepted and implemented.

Rural Medical Relief

The age old problem of Rural Medical Relief has been agitating the minds of Governments and the public. We have not yet found a satisfactory and feasible solution.

A genuine spirit of service to suffering humanity should really activate the members of this noble profession, who should always try to emulate the examples set by eminent doctors like Dr. Scudder, Dr. Somerville and Dr. Allen and others, but for whose pioneering efforts and self sacrifice the very popular and large mission hospitals at Vellore, Ranipet, Madurai would not have come into being.

I feel that doctors who are young and newly married and those who are on the eve of retirement can without much difficulty be posted to serve in rural areas. The Government should go a step further and make it incumbent on every new entrant into service to agree to work in rural hospitals for at least 3 years. Attractive scales of pay should be given, just sufficient to fulfil their social obligations in rural areas and to keep their body and soul together.

In Andhra Pradesh about 2000 doctors are now working in rural parts including service people. It will be one doctor for nearly 10,000 people, a far cry, from the Bhore Committee recommendations of a doctor for every 2,000 people.

The way to attain this recommendation is to start a good number of Primary Health Centres. These units are supposed to function as institutional and domiciliary medical units including school health. Another thing is to convert the existing rural dispensaries to P. H. centres. All these centres should be under the control of the District Medical Officer and not under Block Development officers.

Another suggestion is to start some sort of Health insurance to the villager under panel system which induces doctors to go to villages. It costs less to the State and will be a democratic way of meeting this problem. It will conduce to a more uniform distribution of the profession in our parts.

Insurance

Health Insurance:

The well-off purchase medical care as best as they can. The poor it is said are given it free as philanthropy. The middle class who form the bulk of the population hang in between the two. They cannot afford to buy medical care and their sense of self respect and dignity does not allow them to seek it as a charity. For such class, though not exclusively Health Insurance scheme on economic basis in big towns with the following salient features will be beneficial :—

1. Free choice of Doctors (from panel) to the insured persons.
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6. Domiciliary visits at nominal rates (Rs. 1 to 3).
7. Insurance fees: Individual Rs. 55/ and Family Rs. 100/- per annum.

The details of the scheme can be worked out according to local conditions by the local I. M. A. branches. It is hoped the public in big towns will make full use of such schemes. The Government and local bodies should generously render all possible and legitimate help to the organisers.

Employees' State Insurance:

The establishment of lasting patient-Doctor relationship would be difficult under service system and would be ideal in panel system. The grievances to the employees towards service system are manifold. Government have further worsened the position by starting a contributory health scheme. The position of doctors in service is very unsatisfactory. In socialistic pattern of society, which is the nation's goal, all the lower income groups will have to be covered by some kind of health insurance, voluntary or otherwise. This scheme will be impossible without bringing independent medical practitioners fully into the picture.

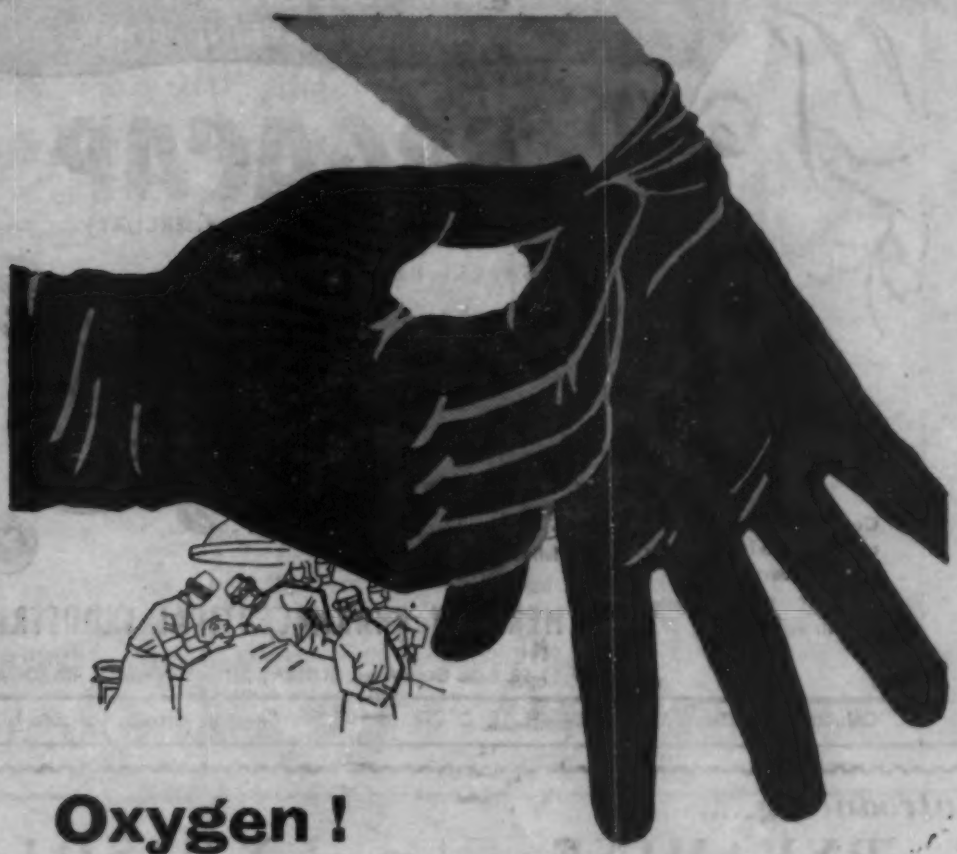
Life Insurance:

The country has welcomed the Nationalisation of the Life Insurance companies, but unfortunately the doctors have been treated shabbily by the new authorities. 70 per cent of Insurance examiners are thrown out without reason. No definite principles are observed in the appointment of new ones. I plead for a more humane approach to this problem.

Five Year Plans

Our Central and State Governments are providing about 8 per cent of the total out-lay under Public Health, whereas in Russia and America it is about 25 per cent. Bhore Committee has recommended 15 per cent in 1946.

The allotment is quite inadequate, considering the backwardness of our State with 32 million population in 20 districts with 200 towns and 2,000 villages. Under the Community Development Programme about 170 Primary Health Centres have been established and an equal number will come up by 1962.



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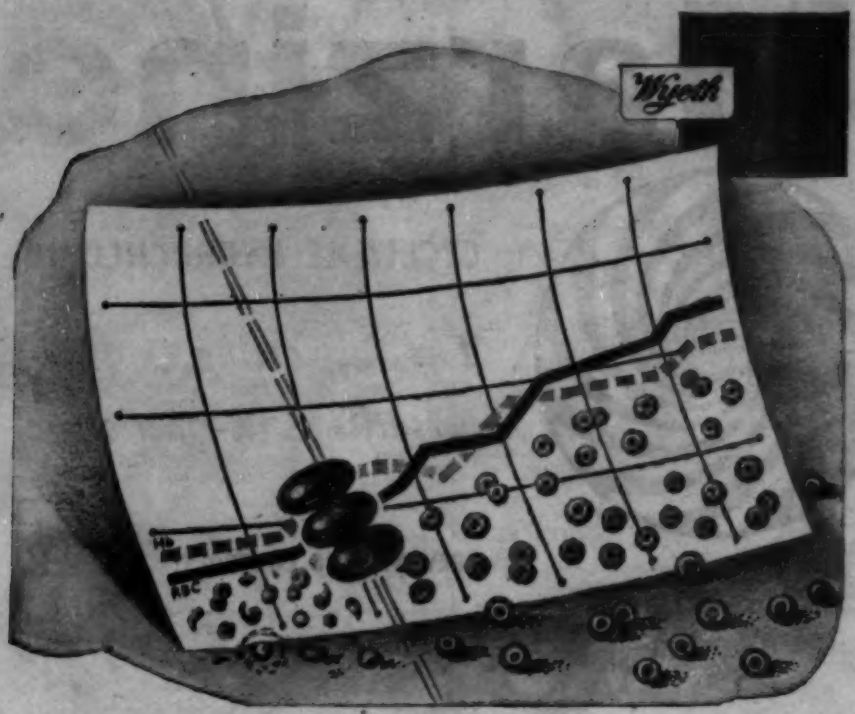

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